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A TEXTBOOK OF

PATHOLOGY

GENERAL AND SPECIAL

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PATHOLOGY
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FOR THE USE OF
STUDENTS AND PRACTITIONERS

BY

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WITH OVER 800 *ILLUSTRATIONS IN THE TEXT AND* 19 *COLOURED PLATES FROM ORIGINAL PREPARATIONS*

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TO

THE MEMORY OF

WILLIAM SMITH GREENFIELD

M.D., F.R.C.P., F.R.C.P.E.,

FOR THIRTY-ONE YEARS PROFESSOR OF PATHOLOGY

IN THE UNIVERSITY OF EDINBURGH, OUR

TEACHER, "CHIEF," AND FRIEND,

WHO DIED AUGUST 12, 1919,

WE RESPECTFULLY AND

AFFECTIONATELY

DEDICATE THIS

BOOK

Since the appearance of the first edition of this work, we have to record with deep regret the passing of him to whom it is dedicated, William Smith Greenfield, whose name will live as one of the great British Pathologists—perhaps, indeed, the father of modern British Pathology.

PREFACE TO THE FOURTH EDITION

THE preparation of the fourth edition of our textbook was commenced more than seven years ago; but the work has been much delayed by serious illness amongst both authors and collaborators; and, more recently, by war-time conditions, including the wrecking of our hospitals by enemy-action: the destruction of the professional part of his house and much material accumulated by one of the authors (W.E.C.D.) specially for this work: and the military service abroad of one of the collaborators (J.O.O.); whilst war-damage in the City of London to the premises of the firms employed has also contributed to the delay. This delay, however, has been of some advantage in that it has allowed of the frequent revision of the whole text, and the embodiment of much new matter from recent medical literature and from our own war-time experience which otherwise would not have been possible.

In this revision, we have had the active collaboration of Dr. A. Murray Drennan, Professor of Pathology in the University of Edinburgh, and Dr. John O. Oliver, Lecturer on Pathology at St. Thomas's Hospital, London. We are indebted also to Dr. Carl V. Weller, Professor of Pathology in the University of Michigan, Ann Arbour, U.S.A., not only for reading the proofs, but for many valuable suggestions which have been incorporated in the text. Our thanks are due also to Dr. J. Douglas Gray, formerly Lecturer on Bacteriology in the University of Bristol, for advice and criticism on the subject of Immunity: to Dr. C. Worster-Drought for the loan of valuable clinical material in connection with the Nervous System: to Dr. W. H. McMenemey, Dr. Colin Edwards, Dr. Leila Hawksley and Miss M. Irene Wilson for help in proof-reading, as well as to numerous other colleagues and friends. We are particularly grateful to Dr. Percival Bailey, Professor of Surgery in the University of Chicago, for the loan of his invaluable neurological diagrams: and to Drs. Dorothy Russell and J. O. W. Bland, of the Bernard Baron Institute of Pathology, London Hospital, for the use of their illustrations of cell-cultures of gliomatous tumours We have also to thank Dr. Edith K. Dawson, of the Royal College of Physicians Laboratory, Edinburgh, for illustrations and other help in connection with Diseases of the Breast and Ovaries. Under the individual figures in the text, we make due acknowledgment of our indebtedness for many of the illustrations throughout the book: and we thank especially our Technical Assistants, Mr. T. C. Dodds, F.R.P.S. (Edinburgh), Mr. W. A. Nelson (Aberdeen), and Mr. Charles Martin and Mr. Ronald Egan (London), for much skilled help—the two last for their work in the preparation of the West End Hospital material used more particularly for the illustration of the Nervous System. Our thanks are due also to the Editors of the *Lancet*, the *Journal of Pathology and Bacteriology* and the *Journal of Neurology and Psychopathology*, for permission to reproduce illustrations from articles published in these periodicals by ourselves and others.

As in previous editions, we have made free use of the published work of others, with, wherever possible, suitable acknowledgment, but without in any way attempting to give a complete bibliography; and we have used small type and footnotes for matter which, though perhaps not of vital importance in a textbook, we yet thought of sufficient interest to merit inclusion.

We have made considerable additions—sometimes, it must be confessed, with reluctance—as well as deletions and textual alterations throughout the book. New Chapters have been added on Viral Infections, Vitamin-Deficiency Diseases, and Diseases of the Female Reproductive Organs. The Chapter on the Nervous System has been completely recast and rewritten, considerably extended, and fully illustrated [1]; that on Diseases of the Blood and Blood-Forming Organs has been extensively revised, as have also the Sections dealing with Retrogressive Changes, Diseases of the Endocrine Organs and of the Kidneys. The Chapter on Granulomata has been re-arranged, and in it the lesions occurring in most of the organs and tissues in tuberculosis and syphilis have been collected and described, except in a few instances in which we thought it advantageous to deal with them under the system, organ or tissue attacked.

We are particularly fortunate in our Publishers, Messrs. William Heinemann (Medical Books) Limited, who have always been ready, often at considerable inconvenience and expense, to make frequent and sometimes extensive revisions for the insertion of numerous alterations and additions which became necessary as the result of newly-published work ; and we wish to thank especially Miss Jean Michie, of that firm. But for her constant and indefatigable help under the most trying war-time conditions, it would have been almost impossible to steer the book through the press. Similarly, our grateful acknowledgments are due to Mr. George Brown and the firm of Messrs. John Swain & Sons Limited, of the City of London, to whose skill we are indebted for the quality of our new illustrations : to the Whitefriars Press Limited, of Tonbridge, for their patience and accuracy in setting and re-setting the text many times : and to Mr. W. J. Bishop for the careful compiling of the index.

Lastly, in this preface, we would welcome the general trend of pathology to become a science of the living, rather than a record only of the end-changes of disease as seen in the post-mortem room, important and instructive as these always are. In our first chapter and elsewhere, we emphasise the importance of study by supravital staining and biopsy-methods and the application of these to early and rapid diagnosis, for example, during the actual progress of a surgical operation. The following extract from the records of the Mayo Clinic,[2] with which we are in complete agreement, emphasises another aspect of recent advances both in pathology and clinical medicine not yet fully recognised : " The further we go in our attempts at early diagnosis of diseases the more and more difficult it will become for clinicians and pathologists to make correct detailed pathologic diagnoses. The history of the Clinic reveals that we are making questionable diagnoses much more frequently—not because we know less but because we are always looking for the earliest stages of disease and not waiting for textbook pictures before attempting to do something beneficial for the patient."

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[1] The indebtedness of one of the authors (W.E.C.D.) to the Medical Research Council for grants towards the investigation and illustration of Tumours of the Central Nervous System is gratefully acknowledged on pages 950 and 1059.

[2] In an article which refers to the difficulty of making an early diagnosis of Hodgkin's disease, in the *Proceedings of Staff Meetings of the Mayo Clinic*, 1938, **13**, 618-623.

POSTSCRIPT. Because of increasing war-time difficulties and restrictions, our textbook has now been in paged-proof form for over three years, and it has been a very difficult undertaking, without unduly disturbing the set-up and pagination of the text, to keep it up to date—an undertaking for which one of us (W. E. C. D.) has alone been responsible. He therefore asks the indulgence of our readers; and, if they find any errors or discrepancies in the text, he will be more than grateful if they will send him a note of them.

J. MARTIN BEATTIE.
W. E. CARNEGIE DICKSON.

September, 1943.

PREFACE TO THE FIRST EDITION

If any excuse were necessary for adding another to the many textbooks of Pathology, it would be found in the fact that the present volume is based on the teaching of the Edinburgh school. This school, in which the first chair of Pathology in the United Kingdom was founded, has sent its teachers and students to all parts of the world, and thus of necessity has had a considerable influence in moulding pathological opinion. In spite of this, some fundamental points which have been taught in Edinburgh for years, and which are founded on careful experimental investigations, combined with a very extensive experience in human morbid anatomy and morbid histology, have not, we think, received sufficient attention. To mention only two points—on infarction much is yet taught which is quite in opposition to experimental investigations; and the relation between certain diseases of the kidney and arterial degeneration seems to be very imperfectly understood.

The book is intended primarily as a textbook for medical students and practitioners, and we have, therefore, dealt fully with the more important and fundamental points in Pathology, and have either omitted altogether or dealt very briefly with rare and unimportant conditions. Minute microscopic anatomy of abnormal structures and tissues has been dealt with—though sometimes briefly, for we fully recognise that no descriptive writing can be substituted for the actual specimen and the microscope, and, moreover, the subject is fully dealt with in textbooks on Morbid Anatomy and Histology. In dealing with animal parasites, much of the minute morphology has been omitted. Bacteriology is so well dealt with in the many excellent textbooks now published, that, important as it is to, and inseparable though it be from, Pathology, we have omitted it altogether as a separate subject.

We have especially to thank our old teacher and chief—Professor Greenfield, of Edinburgh University—for placing the notes of his lectures at our disposal. At his suggestion the work was undertaken, and without his hearty co-operation and the benefits of his wide experience it would have been impossible for us to undertake it. To acknowledge his help is to us a pleasure, but it is, perhaps, even a greater pleasure to have the opportunity of again bringing forward views founded on the results of careful observation and experiment, which he has previously published and taught for many years, but which have not received the attention and recognition which they merit.[1]

The compilation of a complete bibliography has not been attempted, though reference has been made to some of the more important papers consulted.

Almost all the illustrations are new, and are from specimens either specially prepared by or for us, or kindly lent for this work. The great majority of the photo-micrographs are the work of Mr. Richard Muir,[2] Demonstrator of Pathological and Bacteriological Methods in the University of Edinburgh, and we desire to thank him for the care and trouble he has taken in their selection and preparation, the majority of the microscopical specimens being from his private collection. The photographs of practically all the naked-eye specimens were taken personally by one of us (W. E. C. D.), and, where not otherwise acknowledged, are from specimens in his own private collection.

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[1] *See*, for example, pp. 505 and 676, and footnote on p. 681.

[2] This applies to the first edition only.

Lastly, it is a pleasure to acknowledge the uniform kindness and courtesy which we have received from our Publishers in connection with this work, and we thank them for the great care which they have bestowed upon its production.

J. M. B.
W. E. C. D.

October 1908.

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ERRATA AND CORRIGENDA 1368

ERRATA AND CORRIGENDA

P. 178, last line of first footnote: *for* " pcnding " *read* " pending."

P. 315, line 8 from top : *for* " primitve " *read* " primitive."

P. 481, line 17 from top : *for* " lower " *read* " outer."

P. 481, line 27 from top : after " over " at end of line, insert hyphon (" over- ").

P. 505, line 20 from top: *for* " Klebs-Lœffler " *read* " Klebs-Loeffler."

P. 589, last line, *after* " developed " *and before* " agglutinins " *insert* " anti-**Rh**."

P. 622, line 25, and p. 1001, line 5 from bottom of page: for "*Listerella*" *read* "*Listeria*" *monocytogenes*, as amended in 1940 by J. H. Harvey Pirie. This organism has now been isolated from certain cases of *infective mononucleosis* (Robert A. Webb, *Lancet*, 1943, *ii*, 5).

P. 623, line 17 from top: *for* " Löffler's " *read* " Loeffler's."

P. 683, line 13 from bottom: *for* " GLANDULAR FEVER *or* INFECTIOUS MONONUCLEOSIS " *read* " GLANDULAR FEVER *or* INFECTIVE (*or so-called* " *Infectious* ") MONONUCLEOSIS."

P. 1296, column 2, line 1, *for* " **Endoctrine** " *read* " **Endocrine.**"

P. 1305, column 2, line 32, in " explanation of, leukæmias " delete comma.

P. 1316, line 36, *for* " **Klebs-Lœffler** " *read* " **Klebs-Loeffler.**"

P. 1327, 6th line from bottom, *for* " *unerd* " *read* " *under.*"

P. 1351, column 2, line 7 from bottom, *for* " 569 " *read* " 568A."

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PATHOLOGY

CHAPTER I

THE CELL IN HEALTH AND DISEASE

"*Omnis cellula e cellula.*"—Rudolf Virchow.
But: "*each particular organ holds its place . . .*
combining with the rest into one symmetry. . . ."
—John Henry Newman.

The tissues of the animal body, as well as those of vegetable organisms, are composed of cells and their products, and it is essential therefore that, for the study of the tissues in health and in disease, the elementary facts concerning cell-structure and function should be understood as thoroughly as our present-day instruments and knowledge of optics and chemistry will permit.

The classical knowledge concerning the cell was derived from the study of dead tissues, but, more recently, the introduction of methods of tissue-culture has allowed to some extent the direct observation of cellular life. Cinematography has also been used as a method of recording the cellular changes in tissue-cultures, and provides a ready means of reviewing within the space of a few seconds the changes occurring over long periods of time, since the pictures which are recorded at considerable intervals of time on the cinematographic film are viewed in rapid succession by means of the usual projector. Further, the study of biochemical and biophysical changes in cells has added considerably to the older knowledge of cell-life and metabolism.

In the study of all physiological and pathological processes, we must for the present regard the cell as the ultimate biological unit—at the same time a unit of structure and a unit of function—however complex the tissue or organ built up of these cell-units may be. This great truth was first put forward by Schleiden in 1838, and by Schwann in 1839, but it was not until after the publication of Virchow's epoch-making work on Cellular Pathology in 1855 that these fundamental facts were generally accepted in the realm of pathology, and it was recognised that all the functions of the body are the result of, and are dependent upon, the sum of the varied activities of the innumerable cell-units of which the body is built up.

A multicellular organism, whether plant or animal, may be regarded theoretically as a vast colony of unicellular units, but it is only in a very limited sense that the individual tissue-cell can be looked upon as an independent unit. All grades of independence—or perhaps, more accurately, inter-dependency—may be found, from the highly differentiated and fragile nerve- or secretory-cell, which may die almost immediately after removal from its normal environment, up to the all but independent leucocyte, which can live for hours, or even days, if kept in suitable surroundings after it has been removed from the living body. But even the wandering phagocyte, which may be kept alive *in vitro*, cannot be regarded as an independent unicellular organism, and it soon perishes from lack of suitable nutriment which should be elaborated for its use by other specialised cells of the body, or it is poisoned by effete substances of its own formation which should be removed by the highly endowed cells of the excretory organs, co-operation being essential to the common welfare. It is, therefore, more profitable " to regard the organism as the individual, with a common life running through it all, and the cells not as units of which it is built up, but rather as parts into which it is divided in order to provide for the necessary division of labour involved in so complex a process as life. The conception of the cell thus remains, but no longer requires or is capable of the strict definition that was needed when the word was supposed to represent a fundamental biological entity." [1]

GENERAL MORPHOLOGY OF THE CELL

In shape, the animal cell, when examined in tissue-sections or in fixed films, varies indefinitely with such factors as the type of tissue in which it occurs, and the density and nature of the surrounding structures. It may be spherical or ovoid, spindle-shaped, cylindrical or polygonal, or in many types of cell entirely irregular. In living cells, there is often active change of shape from time to time, not only with growth, but with variations in their functions. This is true not only of such cells as muscle-fibres or amœboid leucocytes, where it is a well-established fact, but also of nerve- and endothelial cells, where its occurrence is not so widely recognised.

Protoplasm, the essential material of which the cell is composed, and in which the physical manifestations of the vital processes which are carried on in it occur, is a soft, viscid, colourless, transparent or translucent fluid material, the detailed structure of which, in the living state, is seen microscopically only with great difficulty.

There is no general agreement among histologists concerning the ultimate " structure " of protoplasm, and some of the appearances described as evidence of " structure " may well be no more than those met with in all colloid fluids.

In some animal cells, more especially in certain of the primitive unicellular organisms, the cytoplasm may show differentiation into distinct, more or less concentric, zones : an inner and apparently less highly differentiated zone immediately around the nucleus, termed the endoplasm : and an outer zone, the ecto- or exo-plasm, in which most of the so-called " cell-organs " and other highly differentiated structures, such as the mitochondria, the Golgi-apparatus and the centrioles, are found. In addition, accumulations of proteins, fats, carbohydrates, pigments and secretory granules forming the so-called metaplasmic "inclusions" are also present. In man and the higher animals, this differentiation into cytoplasmic zones is well seen in the case of the giant-cells or megakaryocytes of the bone-marrow (Fig. 361, p. 601).

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[1] Doncaster, " An Introduction to the Study of Cytology," Cambridge University Press, 1920, p. 3.

The centriole (at one time known as the "attraction-sphere"), has been called the dynamic centre for the reproductive activities of the cell, as it is the functional structure which leads the way in mitotic division. It is situated, as a rule, in the endoplasm or innermost zone of the cytoplasm, immediately outside, and often towards one pole of, the nucleus. Sometimes it is single, but more commonly there are two centrioles placed close together, and surrounded by a common envelope from which delicate thread-like rays may be seen radiating into the surrounding cytoplasm, especially when the process of cell-division is about to begin. The centriole or centrioles, together with the surrounding envelope, form the centrosome. In the vegetative condition of the cell, the centrioles lie passively side by side; but, with approaching nuclear division, they diverge from one another, each taking up its position at an opposite pole of the dividing cell; and the fibrils stretching between them

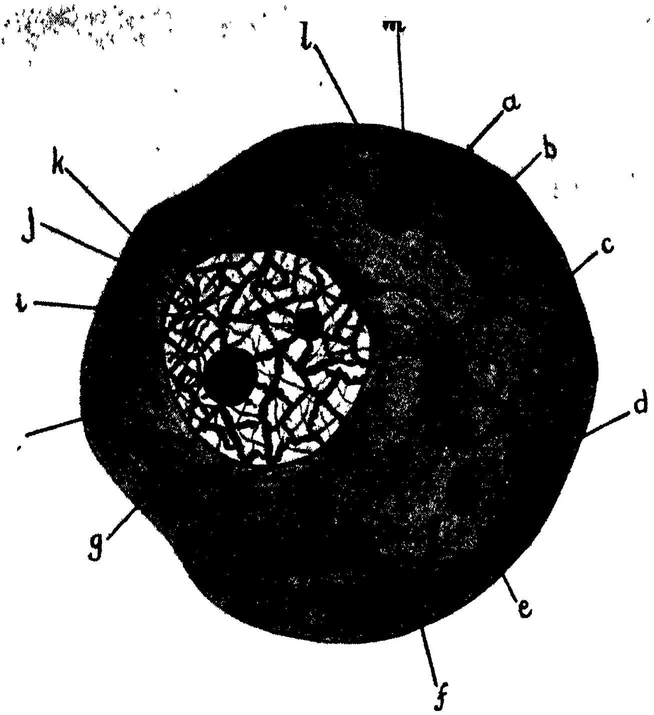

FIG. 1. Diagrammatic Representation of Cell-structure.
(Modified from Wilson, Carleton and Maximow.)
a. Cell-wall or membrane.
b. Cell-protoplasm or cytoplasm.
c. Golgi's reticular apparatus.
d. Vacuole in cytoplasm.
e. Metaplasmic inclusions.
f. Mitochondria of dot-like, rod- and thread-shaped forms.
g. Nucleus.
h. Nucleolus (or plasmosome).
i. Karyosome (subsidiary nucleolus).
j. Chromatin of nucleus.
k. Linin-meshwork of nucleus.
l. Centriole. } (These are usually nearer the nucleus
m. Centrosome. } than shown in the diagram.)

form the achromatic spindle to which the chromosomes of the nucleus become attached after they have divided.

Mitochondria[1] are found in all cells and occur as small granular, rod-shaped or filamentous bodies which are observed most readily when living cells are examined microscopically with dark-ground illumination. Such bodies appear to be motile within the cytoplasm and to undergo segmentation and reunion. It is believed that mitochondria give rise to intra-cellular substances such as enzymes. Mitochondria can be differentially stained by means of Janus-green.

The Golgi-apparatus, demonstrable by silver-impregnation methods, or by prolonged treatment with osmic acid, consists of a network, or a system of rodlets, in the cytoplasm near the nucleus. Its nature and functions are not yet fully understood, though various changes are observed to occur in it during cell-division, and it is almost certainly concerned in metabolism within the cell.

"Vacuoles." In many living cells, *e.g.*, in leucocytes, small, clear, apparently structureless and "empty" areas may often be observed. These are sometimes rather erroneously called "vacuoles," and may be either temporary, especially in actively-functioning cells, or in some cases more or less permanent in their nature. An important type of "vacuole" is that formed around a foreign body which has been englobed or taken into the cytoplasm of the cell by the process known as phagocytosis. A clear space may be observed round such an "included" object or its remains, and this in reality constitutes a little stomach, or "digestive vacuole" as it is called, within the protoplasm, in which the processes of intracellular secretion and assimilation go on in a way precisely analogous to those of extracellular peptic and other forms of digestion. Such "vacuoles" are often specially well seen in the large mononuclear cells or macrophages of inflammatory exudates, and in certain protozoal parasites such as amœbæ.

Another important variety of "vacuolation" of the protoplasm, which occurs, not only in the cytoplasm, but also in the nucleus, is due to degenerative alterations in the reticulum in disease. This will be described more fully later.

Metaplasmic inclusions, the products of secretion and excretion, are found stored temporarily within the cytoplasm until they are required by the organism, or until they can be eliminated by excretion; whilst in other instances the so-called "granules" and other substances appear to be more or less permanent constituents of the cell. In the former of these groups may be placed granules or globules of various fatty substances, glycogen, and other food-elements. The secreting-cells of practically all glandular organs contain in their cytoplasm numerous granules which may be demonstrated by appropriate staining methods. Other cells of importance in this connection are the granular leucocytes of the blood, which owe their present classification to the size and staining affinities of the granules in their cytoplasm. The precise chemical nature of these granules has not yet been determined, though many of them are probably compounds of albumin with other substances, *e.g.*, in the form of nucleo- or gluco-protein bodies, etc.

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[1] Mitochondrion, from Greek *μίτος*, *mitos*, a thread, and *χονδρίον*, *chondrion*, diminutive of *χόνδρος*, *chondros*, a grain or granule.

Such cell-granules are at present classified very roughly into groups, according to their affinity for various acid, neutral, and basic dyes (*cf.* p. 10) :—

i. **Oxyphil** (also called **eosinophil** or " **acidophil** " [1]), with affinity for the acid or protoplasmic dyes.
ii. **Basiphil,**[2] with affinity for the basic or nuclear stains.
iii. **Neutrophil,** with no special affinity for either.
iv. **Amphophil,** with an equal affinity for both acid and basic dyes.

Pigment in granules and particles may be present in various forms in the cytoplasm. In addition to the normal pigment found in cells of the skin, eye, etc., coloured matter may be found in the form of englobed foreign particles, or waste-products of cell-activity. The presence of foreign bodies such as bacteria, and other parasitic organisms, blood- and other cells, is described under **Phagocytosis** (pp. 28, 32 *et passim*) ; and the presence of various degeneration-products, such as droplets of colloid or mucinoid material, fat and oil, etc., is discussed in the chapter on **Degenerations and Infiltrations** (p. 189).

Nucleus. In the typical metazoön cell, there is usually a single nucleus, the executive centre for the control of the constructive and functional activities of the cell—a more highly evolved part of the protoplasm found in all except the lowest living forms.

In some cells, for example in those of the liver, there are frequently two nuclei present, but this may be merely evidence of as yet incomplete or imperfect cell-division. In another important series of cells, for example the osteoclasts, giant-cells and other cells which are concerned more especially in the local absorption of bone, fibrous tissue, pathological substances, foreign bodies, etc., as well as in the giant-cells found in morbid conditions such as tuberculosis (tubercle giant-cells), and in certain tumours, large numbers of nuclei may be found.

The shape of the nucleus varies greatly in different cells, not only according to the class of tissue to which these cells belong, and at different periods of their growth, but also from time to time according to the variations in the state of their functional activity. In some cells, especially after fixation by various chemical or physical methods, the nucleus is more or less regularly rounded or ovoid in outline, and situated approximately in the centre of the cell. In other instances it is indented or kidney-shaped, or, again, it may be highly irregular in its configuration, as in the polymorphonuclear leucocyte of the blood.

One of the most complicated nuclear forms is that found in the megakaryocytes or giant-cells with single hollow basket-like nuclei found in the bone-marrow (Fig. 361, p. 601). Change of nuclear configuration in a developmental series of cells is well exemplified in the granular myelocytes, or marrow-cells, and in the transitional myelocytes formed from them preliminary to the development of the ordinary polymorphonuclear leucocytes of the blood

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[1] Hybrids such as " acidophil " and " ovalocytosis " (p. 661) are best avoided, but some of them have unfortunately become established in pathological literature (*cf.* footnote on p. 641).

[2] Often spelt " basophil," but, as the word is derived from the Greek *βάσις, βάσεως, basis, baseōs*, it should, as above, be spelt with an " i," as in the English words " bas*i*c," " bas*i*city," and " bas*i*lar." (*Cf.* footnote on p. 623.)

(Fig. 373, p. 620). Or, again, in the development of connective tissue, the younger or more primitive actively-dividing cells are rounded in shape and possess rounded nuclei large in proportion to the size of the cell. These cells first enlarge somewhat, and then gradually become elongated until they assume a spindle-shaped outline, the nuclei undergoing a parallel series of morphological changes until they finally assume a rod-like shape. An analogous series of changes may be observed during the development of young muscle-cells.

The relative position of the nucleus within the cell is of some importance, but it must be recognised that, during life, the nucleus may move actively from one part of the cell to another. Changes in the position of the nucleus are of importance in connection with the process of cell-division, whilst an eccentric position of the nucleus is characteristic of certain forms of cellular degeneration, for example in nerve-cells.

Structure of the Nucleus. In the ordinary vegetative condition—sometimes misleadingly called the "resting-stage," in contra-distinction to the changes which are discussed on p. 7 under the subject of cell-division or mitosis—the nucleus presents a more or less definite, typical structure, the component elements of which may be described as follows :—

Nuclear Membrane—a thin, delicate, and usually perfectly transparent structure enclosing the nucleus, and composed of an achromatic substance, that is to say, a substance without special affinity for the dyes or stains used in the study of the cell under the microscope. This achromatic substance is possibly allied to linin or achromatin, one of the constituents of the nuclear network described below.

Nuclear Network. The body or interior of the nucleus is composed of a reticulum or network, in the meshes of which is a clear fluid or nuclear juice. In the nuclear network, the filaments are composed of an unstainable substance called linin or achromatin, along the course of which are attached or embedded granules or small masses of a material which has an intense affinity for certain dyes, and hence is called chromatin. At the nodes or junctions of the nuclear network, the chromatin is sometimes aggregated into larger masses which stain deeply, and are termed net-knots or karyosomes. These are not separate structures ; they stain intensely, as does the rest of the chromatin, with the basic or nuclear dyes ; and must be distinguished from nucleoli, the staining affinity of which is for the protoplasmic or acid dye.

The **nucleolus** or **plasmosome** is a structure which is found embedded or suspended in the nuclear network. It is usually single, but frequently two, and sometimes three, four, or even five, of these structures may be found in one nucleus.

Cell-Wall or **Membrane.** Many cells, *e.g.*, leucocytes and nerve-cells, have either no cell-membrane or possess on their surface only an exceedingly delicate layer of specially adapted protoplasm representing it in function and position.

In some situations there may be direct structural continuity of the cytoplasm of adjacent cells. This may be incomplete or partial, as in the case of the cells of the Malpighian layer of the epidermis, in which the cell-bodies of neighbouring cells communicate by means of the intercellular bridges, giving rise to the prickle-like appearance characteristic of these cells (Fig. 168, p. 336); or, again, this union may be more or less complete, as in the case of the so-called syncytial layers or masses of protoplasm which possess numerous nuclei, but have little or no differentiation of their protoplasm into separate cell-units.

CELL-DIVISION

For full descriptions of the highly complex subject of cell-division, reference must be made by the reader to special works upon the subject,[1] but the question has such important bearings on certain branches of Pathology that a brief outline of the process may be given at this point, special emphasis being laid upon certain of its abnormal or pathological variations. If the student has an opportunity of viewing the instructive cinematographic films made by the late Dr. Canti, he will have no difficulty in seeing in actual motion every one of the series of changes which occur in the division of cells.

Cell-division may take place under the action of various forms of stimulation, physiological and pathological. From the first division of the impregnated ovum onwards, there is the phenomenon of tissue-growth and maintenance. In some cells, for example in the hæmopoietic cells of the bone-marrow, it continues more or less actively throughout life. Nerve-cells, on the other hand, probably do not multiply under ordinary circumstances, if at all, after an early period of life. Many types of cell are capable of actively proliferating under the stress of any special call for their increased activities—notably connective-tissue, endothelial, and other cells which take part in the repair of tissues after injury or damage by disease.

Two methods of cell-division—direct and indirect—are described. Direct, or amitotic division, is said to be brought about by direct fission of the nucleus and protoplasm, and, if it does actually occur at all, is so rare that we need not further consider it.

Indirect division, or cell-multiplication by mitosis, if not universal, is certainly the usual method.

The two fundamental factors in this mode of cell-multiplication are (1) the arrangement of the chromatin into loops or chromosomes, and the cleavage of these into two; (2) the rearrangement of the subdivided chromosomes in the daughter-nuclei. To all the phenomena occurring before and leading up to the division of the chromosomes, the term **Prophase** is applied. To the actual splitting of the chromatin-loops the name **Metaphase** is given. This is followed by the **Anaphase,** during which the daughter-nuclei are built up; and the process is completed during the **Telophase,** in which the cell-body becomes divided into two daughter-cells. A tabular scheme of these phases, and the accompanying series of diagrammatic figures, may aid in the explanation of this complicated process.

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[1] Darlington, "Recent Advances in Cytology," Churchill, London, 1933; Gray, "Text-book of Experimental Cytology," Cambridge University Press, 1931; Schafer's "Essentials of Histology" (Edited by Carleton), 14th Edition, Longmans, London, 1938.

MITOTIC DIVISION

The stages in regular mitotic division are set out in the following diagrams :

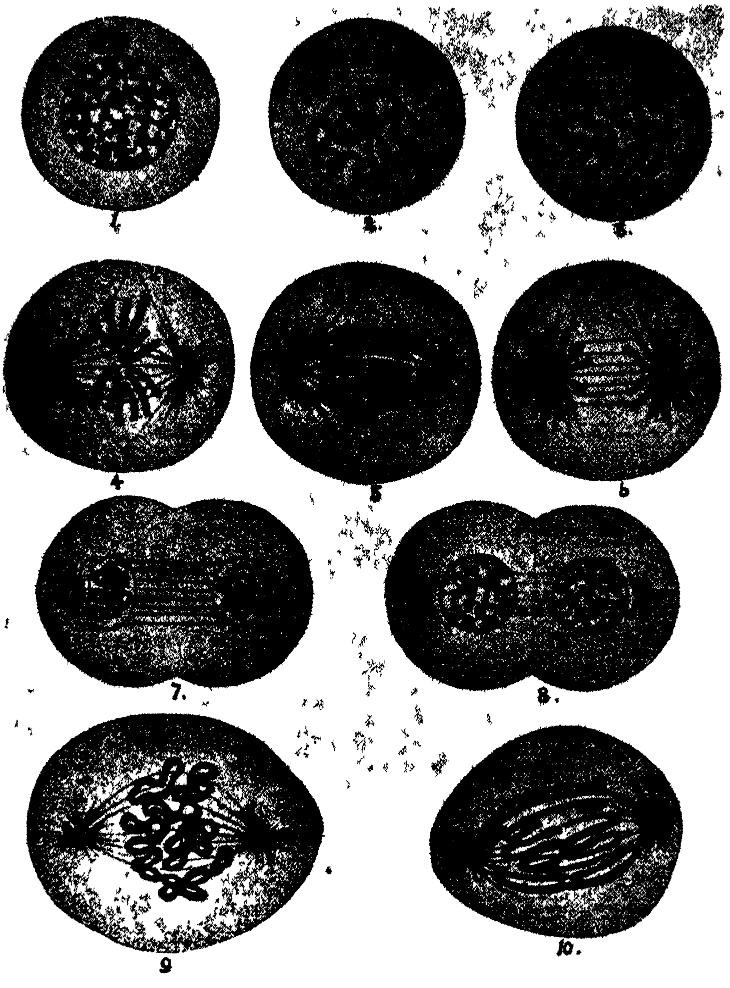

Fig 2. Diagrammatic Representation of the Processes of Cell-division.

1-8 Mitosis in Somatic Cells
1 Cell during *vegetative period* The centriole has already divided
2 *Prophase* Division of attraction sphere, formation of achromatic spindle and spireme
3 *Prophase* Breaking up of spireme into chromosomes
4 *Metaphase* Splitting of the chromosomes after their arrangement around equator of the spindle during prophase
5 *Anaphase* Halves of divided chromosomes passing towards poles of spindle
6 *Anaphase* Chromosomes at poles of spindle
7 *Anaphase* Chromosomes united into spiremes Formation of nuclear membrane round daughter nuclei This diagram also shows commencement of telophase
8 *Telophase* Final stage, with division of cytoplasm The new centrioles have already divided
9, 10 Mitosis in Gametogenetic Cells
9 Formation of ring shaped chromosomes in *Hetero type Mitosis*
10 Their division and passage to poles of spindle

MODIFICATIONS OF THE PROCESS OF CELL-DIVISION BY MITOSIS

1. One of the most remarkable modifications of the process of cell-division by mitosis is that known as meiosis, or **reduction of the chromosomes** during the maturation of conjugating germ-cells The ordinary process of cell-division, as it occurs in the general somatic or body-cells, is characterised by the formation of a definite, specific number of chromosomes. Thus, in the case of the human subject, there are said to be forty-eight of these

bodies formed in ordinary somatic mitosis. In the case of each of the conjugating germ-cells, or male and female gametes—the ovum and spermatozoon—the number of chromosomes is reduced to one-half the original number, in order that, in the resulting single cell—the impregnated ovum or zygote—formed by the union of these two elements, the number of chromosomes characteristic of the species may remain constant. Were this process of reduction not carried out during the maturation of these conjugating cells, the number of chromosomes would become progressively doubled at each union. As we have just noted, to the process of cell-division characterised by this reduction of the chromosomes to half their original number, the term **meiosis** is applied, in contradistinction to ordinary somatic mitotic division. The pathological interest of this variety of cell-division lies in the fact that, by certain writers, its occurrence has been described in some malignant neoplasms ; and that various hypotheses as to the possible origin of tumours have been based largely upon this alleged similarity to the processes occurring in gametogenetic cells from which are derived the mature gametes or conjugating germ-cells. For a full description of the mechanism by which the reduction of the chromosomes is effected, reference should be made to works on embryology and cytology.

Other modifications of the mitotic process may be summarised as follows :—

2. **Heterotype Mitosis,** in which the halves of each of the dividing chromosomes at first remain united at their ends, giving rise to a series of ring-like bodies. This variety of mitosis is seen in gametogenetic tissue during the development of germ-cells and results in a reduction of the number of chromosomes in the nuclei of the daughter-cells. It is important from the fact that its occurrence has been described in some malignant tumours.

3. **Pseudo-reduction** may occur in certain somatic cells, and is probably explained by the fact that two of the chromosomes remain united together.

4. **Asymmetrical Mitosis,** where the chromosomes are unequally distributed between the two daughter-nuclei, or where some of the chromosomes are destroyed after their formation. Such asymmetrical mitoses are common in certain tumour-cells, especially in carcinomas, and may be accompanied, and perhaps caused, by an asymmetrical development of the centrosome and spindle. This type of mitosis has also been induced artificially by the application of certain chemical substances.

5. **Multipolar Mitosis,** in which the spindle may possess three, four, or perhaps even more poles, at which corresponding nuclei are built up. This method is said to occur normally in certain vegetable cells ; but in the animal cell it is entirely pathological, and is due probably to a premature splitting of the centrosome, or to one or both of the daughter-nuclei at once going on to another division. Such multipolar mitotic figures have been found especially at the growing margins in some forms of malignant tumour. (Figs. 127–8, p. 276.)

Experimental work in America upon the influence of certain drugs, particularly colchicine—the alkaloid derived from *Colchicum autumnale* or meadow-saffron—upon the cell-division of some garden-vegetables and other plants and flowers, is yielding interesting results in the direction of the modification of the number of the chromosomes, sometimes doubling or even quadrupling them, and leading occasionally to the production of important **mutations** and **hybridisation** affecting growth and resistance against disease.

THE CHEMISTRY OF THE CELL

As it is impossible to deal at all adequately with questions of cellular chemistry in a book devoted to Pathology from the general point of view, the student is advised to consult text-books on biochemistry on this subject.

STAINING-PROPERTIES OF THE VARIOUS CELL-ELEMENTS

The study of the cell-constituents is dependent largely on their reaction to certain dyes and other chemical substances, and this study has been considerably facilitated by the technique known as vital staining (*see* opposite).

The reagents which are most commonly used for the purpose of staining microscopical sections of tissues may act either physically or chemically. The latter method is that which occurs in the case of the most important group of reagents used for this purpose, viz., the aniline dyes.

Under suitable conditions, chemical union of these dyes with the tissue-elements can be brought about, some structures possessing a greater affinity for those of the basic, and some for those of the acid, series ; whilst other tissue-elements may take up both equally, or have no special affinity for either (*cf.* p. 5). The tissue-elements may thus be classified somewhat roughly into those which are oxyphil, basiphil, amphophil, and neutrophil, respectively. In addition, the term chromophobe has been introduced in connection with certain cells (as, for instance, in the pituitary gland) where it is difficult to induce staining of the cells by any of the usual methods.

Oxyphil (sometimes called " acidophil "[1] : eosinophil). Cytoplasm : centrioles, centrosphere and rays : spindle-fibres : linin-network of the nucleus : nucleoli or karyosomes : certain cell-granules. The more important acid or cytoplasmic stains are eosin and erythrosin, acid fuchsin, light green.

Basiphil.[2] Chromatin and chromosomes, *i.e.*, substances rich in the phosphorus-holding nucleic acid : certain cytoplasmic granules (p. 5). The more important basic or nuclear stains are hæmateïn (combined with alum as " hæmalum "), methylene and toluidin blues, thionin, gentian violet, saffranin, Bismarck brown, methyl and methylene greens, basic fuchsin.

For many years the emphasis laid on methods of staining in histological technique has tended towards a lack of appreciation of the value of observations made on cells, stained and unstained, by the " wet-film " method—although Carnegie Dickson (p. 572), Norah Schuster and others have, for a considerable number of years past, demonstrated the value of fresh-wet-film methods in diagnosis, especially when applied to the examination, not only of urine and fæces, but also of cerebrospinal fluid and puncture-fluids from the brain and elsewhere, and of sputum, in which, by such methods, malignant cells, fragments of new growth and many forms of inflammatory cell are more readily discernible than by the examination of ordinary dried-film preparations.[3]

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[1] See first footnote on p. 5.

[2] For spelling of the word " basiphil " see second footnote on p. 5.

[3] For examples of " fresh-wet films " of cerebrospinal fluids, see Figs. 577–9, pp. 960–2 : Figs. 592–4, pp. 985–7 ; and for specimens of " diagnostic puncture-fluids," see Fig. 128, p. 276 : Fig. 668, p. 1089 : Fig. 704, p. 1117 : and Figs. 735–6, p. 1147 : and of malignant cells in sputum, Fig. 350, p. 572 (with its footnote).

An alternative method is that of Dudgeon and his co-workers, in which rapid fixation of fresh-wet films by Schaudinn's fluid is followed by staining. Here, again, cells are observed by a technique which excludes or minimises the gross autolytic processes involved when tissues or cells are "fixed" by the slowly-acting fixative fluids in general use.

VITAL STAINING IN RELATION TO CELL-FUNCTIONS AND ACTIVITIES

The process known as "**vital staining**" implies the staining of the **living** protoplasm of a cell, and is brought about as the result of an active process on the part of the cell itself. Weak solutions of such dyes as trypan-blue are concentrated within the cells of the reticulo-endothelial system, so that gradually the cells of this system become stained, following the injection of the dye into the blood-stream. Under such conditions, the dye is found in the stained cells in the form of granules, but whether these represent mere particles of dye itself or whether the appearance is due to the staining of certain intra-cellular substances is not known.

Since the process of vital staining calls for active participation by the cell itself, it is hardly surprising that the cells of the body vary in their power of reacting to such a staining-process, and it is those cells which normally exhibit most phagocytic power which are most readily stained by the vital methods, namely, the cells of the reticulo-endothelial system.

From the process of vital staining, that of **supra-vital staining** has been developed. In this, the cells are stained immediately after removal from the body and whilst they are still living. The staining of red blood-corpuscles with brilliant cresyl-blue for the demonstration of reticulocytes (Plate XIV, facing p. 594) is an example of this process of supra-vital staining. Also frozen sections may be made from unfixed tissues immediately after removal from the body, and to such sections, in which the cells are still living, isotonic aqueous solutions of stains such as toluidin or polychrome methylene blue may be applied to accomplish supra-vital staining. The **resistance** of **living cells** to the action of certain dyes, which will stain these same cells when dying or dead, is illustrated in Fig. 592, p. 985.

Note. A short illustrated section on the study, by methods of **artificial cultivation,** of living cells derived both from normal and from pathological tissues, was in course of preparation when war broke out, and has, perforce, been omitted here. A reference to this important subject has, however, been inserted at p. 1125, in connection with the cultivation of the cells of tumours of the nervous system, with illustrations kindly lent to us by Drs. Dorothy S. Russell and J. O. W. Bland (pp. 1126–28).

DEGENERATIVE AND ALLIED CHANGES IN THE CELL

Any or all of the three great groups of cellular activity, viz., (1) growth and maintenance or nutrition, (2) reproduction, and (3) specialised function, may be influenced or interfered with either temporarily or permanently by certain conditions. Most important among these may be placed alterations in the quality or quantity of the supply of nutriment, including vitamins: and exposure to the action of injurious agencies such as excessive heat or cold, pressure, electricity, various forms of radio-activity, or of chemical substances such as organic and inorganic poisons, toxins produced by bacteria, etc. In the histological study of such conditions, the only guides to our knowledge at present available are the actual physical changes brought about in the tissues. The axiom that function and structure are so essentially interdependent that any alteration in the one, however slight, must necessarily mean a corresponding change in the other, is of primary importance. From alterations in the functions of an organ during life we may be able to deduce, sometimes with a comparative degree of certainty, the presence of definite changes in the actual structure of the organ or tissue; for example, the presence of certain abnormal substances in the urinary secretion frequently indicates certain definite structural alterations in the kidney. Conversely, it is often possible, from the consideration of the actual histological changes in an organ or tissue, to infer what abnormalities were present in its functional activities during life: and hence the importance of the correlation of structure and function.

The wide range of structural variations possible in the healthy cell during different phases of cell-activity must be constantly borne in mind, as many of the degenerative conditions affecting the cell are in reality exaggerations of these normal functional variations.

All gradations, from slight stimulation up to total death and destruction of the cell, may be brought about by the same injurious agent, the degree of change depending upon such factors as its amount, intensity, length of application, etc., and also on the capacity of the tissue to resist its attack. Thus the application of some sufficiently dilute toxic substance may cause a stimulation of any or all of the various cell-functions. The earlier changes seen in "cloudy swelling" (p. 190) are in many ways analogous to those seen in the cells of an actively secreting gland. An increase in the number of dividing cells in the part, as evidenced by abnormally numerous karyokinetic figures, is often a characteristic feature of such a condition; and many other phenomena, both cytoplasmic and nuclear, may be regarded as analogous to those seen during increased, or in some cases decreased, functional activity.

Again, the irritant may, from its nature or from the method of its application, be able to kill the cell outright, with little or no change in its visible structure—the condition aimed at when we artificially "fix" a tissue for examination—or in other instances it may bring about great changes in, or perhaps even the total destruction of, the normal structure.

The extreme variability of the results produced by the application of the same injurious agent, in different degrees of concentration or in different amounts, in repeated or in single doses, is very well illustrated in the case of certain chemical substances which are used medicinally. Thus, corrosive sublimate in very minute doses is found to stimulate the reproductive and other activities of a tissue; in larger doses it produces marked toxic changes, such as intense inflammation or actual necrosis; whilst if it is applied locally in concentrated solution, it "fixes," *i.e.*, kills, the tissues outright, with but slight alteration in their morphological structure. Similarly, various salts of mercury, arsenic, lead, etc., when given in small repeated doses, produce at first a very definite stimulation of the reproductive or hæmopoietic activities of the bone-marrow; but, if their administration be prolonged, the stimulating effect wears off, the tissue gradually fails to react, becomes worn out, and undergoes degeneration, accompanied by profound anæmia. This is well seen in cases of chronic lead- or arsenic-poisoning (p. 608).

Thus, in studying the action and results of any particular form of irritant, whether chemical or physical, all gradations between these extremes may be observed, but for our purpose here it will be sufficient to mention some of the more commonly recognised degenerative conditions seen in the cell.

In some instances these degenerative changes are found affecting especially the **cytoplasm,** whilst in other instances it is the **nucleus** which suffers more; but, if they are found in any marked degree in **one** of these constituents, the **other** part of the cell is also almost invariably affected.

CYTOPLASMIC CHANGES

Probably the commonest degenerative condition affecting the cytoplasm is that known as **cloudy swelling,** which will be discussed more fully later (p. 190). The cell-body becomes swollen, perhaps from the imbibition of fluid from the surrounding lymph, and the cytoplasm is physically altered in such a way that a very definite reticulum becomes apparent in it. At certain parts of the cytoplasm, clear vacuole-like spaces tend to appear, due to destructive changes and the accumulation of fluid. These so-called " vacuoles " may increase in size and number until the whole cell-body shows merely as a scanty shred-like network with very slight staining capacity, and finally it becomes broken up and disappears. (Fig. 3, p. 14.)

In other cases, the swollen cytoplasm becomes more homogeneous in appearance, owing perhaps to the imbibition of lymph, *e.g.*, in what is known as **Zenker's degeneration of muscle** (Fig. 117, p. 249 : and p. 1242). This is to be regarded as a " post-necrotic " change, that is, a change supervening **after** the death of the cell; and its occurrence was originally described by Zenker, who observed the condition in the abdominal muscles in cases of typhoid fever. It may be found also in paralysed or in bruised muscle, or in muscle which has been subjected to the action of certain bacterial toxins, *e.g.*, in acute infective fevers, or where such toxins act locally around areas of inflammation. The muscle-fibres lose their transverse striation, become swollen and homogeneous in appearance, and later undergo fragmentation and absorption.

NUCLEAR CHANGES

In the early stages of irritation, *e.g.*, in cloudy swelling, the nucleus may show a distinct preliminary increase in its staining capacity, a condition analogous to that seen in the early stages of mitosis, or in an actively functioning cell before its chromatin has become transformed into the special products of cell-activity. This preliminary increase in the staining capacity of the nucleus forms a well-marked feature in some cell-degenerations, and is sometimes known as **hyperchromatosis.**

In the later stages of cloudy swelling, the nucleus usually becomes progressively paler in its staining reactions, the chromatin apparently becoming dissolved, or at all events so changed in its composition that it loses its affinity for the basic dyes. This apparent solution of the chromatin in the cell-juice is known as **karyolysis** or **chromatolysis.**

Fragmentation of the nucleus, or **karyorrhexis,** is also a common method of nuclear degeneration, and is usually preceded and accompanied by hyperchromatosis. If the nucleus at the same time becomes more condensed in its structure, the term **pyknosis** is applied to the condition—hyperchromatosis and pyknosis being evidently closely allied processes, which are frequently found in conjunction with one another. As the process of karyorrhexis advances, the nuclear network becomes broken up, and its chromatin tends to aggregate into irregular particles or masses. These may exhibit no apparent plan in their method of arrangement, but, on the other hand, they are sometimes found dotted very regularly over the whole nucleus ; or, perhaps even more frequently, they are arranged in a somewhat symmetrical manner around the periphery of the nucleus, being apparently attached to the inner surface of the perinuclear membrane. The latter may then become dissolved, and the chromatin-particles are found scattered in the cytoplasm, in which they undergo solution ; or, if the cytoplasm itself has also broken up, they will be found lying free, for example in the resulting caseous material, pus and other inflammatory and degenerative products of tissue-destruction.

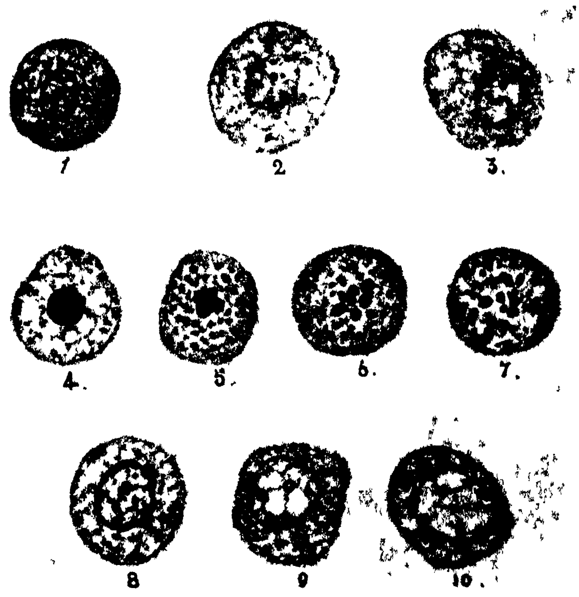

FIG. 3. Cell-degeneration.

1–3, Karyolysis.
4–7, Pyknosis, hyperchromatosis, and karyorrhexis.
8–10, Karyorrhexis.
Cloudy swelling is present in all of these cells.

Another important phenomenon sometimes seen in connection with nuclear degeneration is the production of bud-like processes which are extruded from the periphery of the nucleus into the cytoplasm. These little masses containing chromatin at first retain their affinity for the nuclear dyes, but this becomes gradually lost as the chromatin disappears. This phenomenon may be well seen in the normal development of the erythroblasts or nucleated red blood-corpuscles of the bone-marrow which are in process of losing their nuclei and becoming transformed into erythrocytes or ordinary non-nucleated red corpuscles ; and it may also very often be observed in the erythroblasts which have escaped into the blood-stream in various pathological conditions.

CHAPTER II

INFLAMMATION AND REPAIR

INFLAMMATION

UNDER the term " inflammation " we include both the effects following irritation or injury, and that series of changes which Nature exhibits in her attempt to remove or oppose the cause and repair its results. From the time of the injury until complete healing takes place, the various reactions co-operate with, and are often dependent upon, one another ; and it is generally impossible to draw an absolute line between the end of the active inflammation and the commencement of repair. For the study of the reactions, however, it is convenient to make definite lines of separation ; but it must be understood that these are more or less arbitrary, and that the processes may go on side by side.

Causes of Inflammation. Among the most important of the causes must be placed bacteria and their toxins (*see* section on " Bacterial Infection," p. 124 *et seq.*). After the discovery of the association of bacteria with disease, it became, for a time, almost an article of medical faith and certainly of popular belief that the equation: *Bacteria* + *Man* = " *Disease* " was true in practically all circumstances ; but it soon became evident that many other factors influencing both sides in the struggle which constitutes disease had to be taken into account—conditions favourable to the bacteria in their attack upon the animal body : conditions unfavourable to the latter and weakening its powers of defence and resistance. Experimentally, it has been found that the spores of certain anaerobic bacteria when injected into the muscles of animals will not of themselves produce gas-gangrene (p. 253), but require " help in the form of calcium salts or certain colloidal suspensions to overcome the defences of the body and to release their power to do harm." [1] Moreover, not only bacteria, but other irritants—mechanical, chemical, and physical—which cause tissue-damage will excite the reactions for the prevention of further damage and for the repair of that already produced in the tissues. Even though the injury be extremely slight, protective action and repair are necessary ; and all the inflammatory reactions will exhibit themselves in a more or less pronounced degree. Thus it may be stated broadly that *anything* which causes damage or irritation to the tissues may excite the reactions which are classed under the term inflammation.

The character of the reaction and the degree of its manifestation will, of course, depend on the nature of the irritant and the intensity and duration of its action. Thus, the majority of pathogenic bacterial irritants will call forth a greater leucocytic response than will an aseptic foreign body ; and certain bacteria, or even different strains of the same organism, will elicit a greater response than others. Again, the vitality and the power of reaction on the part of the tissues are of considerable importance. This response of the tissues may be increased or decreased as the result of the presence or absence of vitamins (p. 439 *et seq.*) : of endocrine action (p. 806 *et seq.*) : or of immun (p. 127 *et seq.*). The avitaminosis in scurvy leads to impairment of the pow of the tissues to defend themselves, allows the attack upon them of mic organisms, and is thus indirectly responsible for the inflammatory reaction the gums and serous membranes in this disease. Patients immunised agai diphtheria or scarlet fever exhibit much less severe reactions to infection w the organisms of these diseases than do those who have not been tl immunised. A slight injury may, in some conditions, give rise to seric inflammatory phenomena in tissues the vitality of which is low, whereas normal structures the reaction would be slight. If, however, a tissue exhausted from any cause, its reactive power may be reduced or alm destroyed. For example, in pneumonia, there is usually a very pronounc leucoblastic reaction in the bone-marrow, and a resulting protecti leucocytosis ; but, in certain cases, and, especially in alcoholic subjects, tl reaction may be practically absent, because the bone-marrow is deficient its normal structures and in its capacity for leucoblastic change (p. 621) ; a thus the protective power of the leucocytes is lost, and the prognosis mu more serious.

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[1] " Seed and Soil in Cancer Research," *Lancet* " annotation," 1941, *i*, 546.

Inability of the bone-marrow to produce leucocytes may result from und exposure to radio-active agents such as Röntgen rays. Before adequate pr cautions were taken, pneumonia was particularly fatal in radiologists, whom it frequently ran its course without a protective leucocytosis. Ne interest in this field has been aroused by the demonstration that various su stances such as benzol and certain other coal-tar products used as drugs ma depress the number of leucocytes in the circulating blood far below norma may, in fact, cause them practically to vanish. The use of such terms a "agranulocytosis" and "granulocytopenic angina" indicate the significanc attached to the resulting modification in the processes of inflammatio Under such circumstances the body has but little ability to resist infection.

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If, now, the irritant be removed and the resulting damage be slight, these phenomena gradually subside ; but, if the irritant has caused degenerative or necrotic changes in the tissues, the inflammatory processes may continue until repair is effected. Mononuclear cells of various types now appear in the exudate. These are wandering phagocytic cells which aid in the removal of dead and damaged tissues. New capillaries, formed from pre-existing capillaries, together with proliferated connective-tissue and, perhaps, other cells, pass into the damaged part, and eventually effect a varying degree of repair. From this description of the phenomena of inflammation, it is evident that inflammation in itself is strictly a physiological reaction for the purpose of protecting the tissues against injury by bacteria and other noxious agents, and of repairing damage that has been done by these agents. During the inflammatory process, and especially if the injury has been severe, it has been suggested that histamine or allied substances (pp. 35–6), and metabolic and bacterial poisons, are absorbed, affect the nervous and other systems, and cause fever and other reactions such as leucocytosis.

I. VASCULAR PHENOMENA—INCLUDING THE CHANGES BOTH IN THE VESSELS THEMSELVES AND IN THEIR CONTAINED BLOOD

1. **Initial Vascular Changes.** Omitting the stage of transitory anæmia, with momentary contraction of the vessels, which may occur in certain cases, there is at first an acceleration of the blood-stream, with dilatation of the minute vessels, especially the capillaries and venules. The dilatation of the arterioles is very slight, and seems to play no important part. Some, indeed, hold that it does not occur at all. Even if we deny the occurrence of arterial dilatation, the acceleration of the blood-flow is explained by the dilatation of the capillaries and venules, and the consequent diminished peripheral resistance. This period of **active hyperæmia** (pp. 187–8), which may last for only a few hours, is succeeded by the period of **stasis,** in which there is further dilatation of the vessels and a slowing of the blood-stream. This slowing may become very marked, and, in certain parts, complete arrest may take place, with consequent thrombosis. As the blood-flow becomes sluggish, the leucocytes, which are of less specific gravity than the red blood-corpuscles, tend first of all to fall out into the peripheral stream. If the rate of flow is still further diminished, the red corpuscles also are carried into the peripheral stream, and a mixing of all the elements takes place. This rearrangement of the corpuscular elements is merely a physical phenomenon. The velocity of the axial is always greater than that of the peripheral stream, and the corpuscles circulate in the axial stream as long as the velocity is sufficient. Complete stagnation may be a later phenomenon, and then the vessels appear to be filled with a mass of fused red corpuscles. During this period of stasis, the leucocytes in the peripheral stream become adherent to the wall at various points, and begin to migrate through the coats of the vessels into the surrounding tissues (Plate I, opposite p. 18).

vitamins (p. 439 *et seq.*) : of endocrine action (p. 806 *et seq.*) : or of immunity (p. 127 *et seq.*). The avitaminosis in scurvy leads to impairment of the powers of the tissues to defend themselves, allows the attack upon them of micro-organisms, and is thus indirectly responsible for the inflammatory reaction in the gums and serous membranes in this disease. Patients immunised against diphtheria or scarlet fever exhibit much less severe reactions to infection with the organisms of these diseases than do those who have not been thus immunised. A slight injury may, in some conditions, give rise to serious inflammatory phenomena in tissues the vitality of which is low, whereas in normal structures the reaction would be slight. If, however, a tissue is exhausted from any cause, its reactive power may be reduced or almost destroyed. For example, in pneumonia, there is usually a very pronounced leucoblastic reaction in the bone-marrow, and a resulting protective leucocytosis ; but, in certain cases, and, especially in alcoholic subjects, this reaction may be practically absent, because the bone-marrow is deficient in its normal structures and in its capacity for leucoblastic change (p. 621) ; and thus the protective power of the leucocytes is lost, and the prognosis much more serious.

Inability of the bone-marrow to produce leucocytes may result from undue exposure to radio-active agents such as Röntgen rays. Before adequate precautions were taken, pneumonia was particularly fatal in radiologists, in whom it frequently ran its course without a protective leucocytosis. New interest in this field has been aroused by the demonstration that various substances such as benzol and certain other coal-tar products used as drugs may depress the number of leucocytes in the circulating blood far below normal ; may, in fact, cause them practically to vanish. The use of such terms as "agranulocytosis" and "granulocytopenic angina" indicate the significance attached to the resulting modification in the processes of inflammation. Under such circumstances the body has but little ability to resist infection.

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The slowing of the blood-stream depends on several factors. As a result of the inflammatory process, and from the direct action of the irritant, the endothelial cells lining the vessels become swollen, the intercellular cement-substance becomes loosened, and the cells project into the lumen. Thus a greater frictional resistance to the flow of blood is set up. This friction is probably increased by the adhesion of leucocytes to the walls, and by the greater viscidity of the red blood-corpuscles which are in contact with the walls. Lister showed definitely that these red blood-corpuscles became more viscid, and in consequence more difficult of circulation. In addition to the alteration in their endothelium, the vessels undergo other structural and functional changes. In consequence of the damaged nutrition, their normal elasticity is impaired, and they become unduly stretched. This is more pronounced in the venules than in the capillaries. The dilatation and loss of elasticity lead to an increased intravascular pressure and further dilatation; the blood cannot escape freely from the veins, and tends to accumulate in them. The exudation of lymph has increased considerably during this period of stasis, and an alteration in the composition of the blood-plasma thus arises, and this may be an added factor in the production of vascular dilatation.

2. **Exudation of Fluid.** The increased exudation of fluid is observed very early in the process, and becomes more evident during the first two hours. The resulting inflammatory swelling may supervene rapidly; and its degree is dependent on the situation in which it occurs, on the nature and intensity of the causal irritant, and on the condition of the patient.

In situations where the degree of external pressure is small, or the external support feeble, *e.g.*, in the pleural sacs, large accumulations may take place; whereas in solid tissues or organs the exudate is comparatively scanty. Some bacterial irritants cause an abundant exudation, whilst with others the amount is insignificant. Again, in debilitating disease where there is pronounced anæmia with grave alterations in the condition of the blood and changes in the vessel-walls, the process occurs with greater facility (*cf.* pp. 655 and 668–70). This is due in part to a greater porosity of the vessels, owing to degenerative changes and to the increased pressure in the engorged and dilated vessels. The increased osmotic pressure exerted by the products of the exudate will also attract fluid to the tissues from the blood in the vessels.

Characters and Composition of Inflammatory Exudates. The characters and composition of the inflammatory exudates in different positions and with different irritants vary considerably. The exudate in one cavity may differ greatly from that in another, both in specific gravity and in its coagulability, and that produced by one irritant may show great differences from that produced by another. Inflammatory exudates are richer in protein constituents than ordinary lymph and dropsical transudates, but, unless there has been actual hæmorrhage, the amount of these never equals that of the blood-plasma. Coagulation, though usual, may be absent in certain conditions, *e.g.*, in abscesses or where the cellular content is low. In an abscess, ferments are set free from the leucocytes and tissue-elements and possibly from the bacteria, and overcome the normal anti-proteolytic property of the plasma, whilst in serous exudates the number

DESCRIPTION OF PLATE I

PLATE I

(From thesis by the late J. W. Dawson, M.D.)

FIG. 1. *Longitudinal Section of a Dilated Vessel at the Margin of a Wound* (twenty-one hours). × 700. Note emigration of the leucocytes and their amœboid character.

a. Red blood-corpuscles in lumen of dilated capillary.
b. Polymorphonuclear leucocytes in lumen of dilated capillary.
c. Polymorphs emigrating through wall of capillary.
d. Actively amœboid polymorph which has just escaped from capillary.
e. Lymphocyte (mononucleated cell).
f. Fibroblast.

FIG. 2. *Dilated Vessel at the Margin of a Wound* (six hours after infliction). × 700. Note emigration of polymorphonuclear leucocytes.

a. Lymphocytes fixed in process of emigration through vessel-wall.
b. Similar lymphocytes outside the vessel.
c. Larger forms with indentation of the nucleus.
d. Polymorphonuclear leucocytes.
e. Fibroblast.

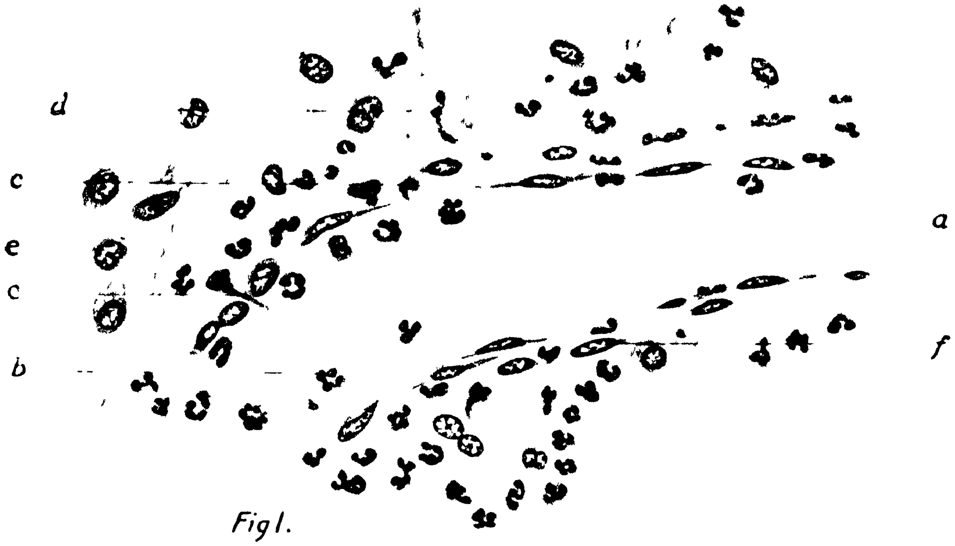

Fig 1.

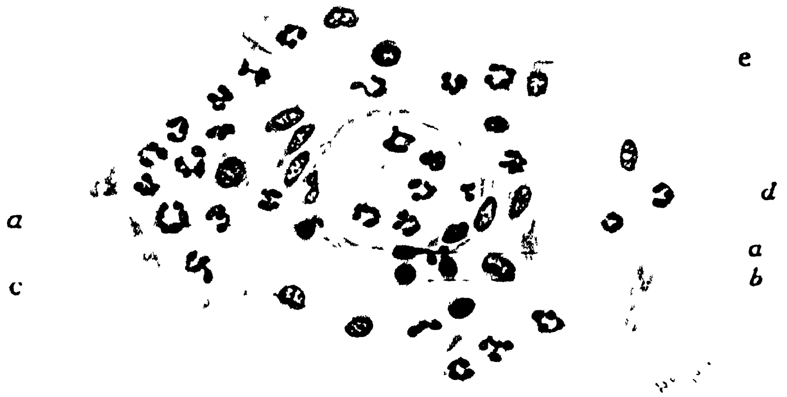

Fig 2.

of cells present may not provide the necessary amount of fibrin-forming substances. The exudates may contain special antitoxic and antibacterial bodies.

Function of Exudates. It is quite probable that, in the process of repair, where there is stimulation of the local tissue-cells, and, in consequence, an increased local metabolism, the exuded lymph may serve for purposes of nutrition ; but we do not consider that this is an important function of the exudate. Much more important is its action in diluting toxic substances, and thus minimising, at all events their local, destructive action. Further, it must act as a flushing-out agent, carrying the poisons, which may be locally produced, either to the surface, to lymph-nodes where possibly they may be destroyed, or to serous cavities. It must be recognised that this mere flushing-out action, though beneficial at the region of irritation, may be harmful to the organism as a whole ; for the poisons, originally acting only locally, may be carried into the general circulation, and thus cause widespread poisoning effects. This flushing, however, acts also by carrying antibodies or protective substances in general,which may be locally produced, to various parts of the system : and by carrying those which are in the plasma into the tissues, and thus thoroughly infiltrating them with these protective substances. The success of Bier's congestive treatment, and, no doubt, also, some of the success gained by Wright in flushing as an aid to his opsonic treatment, are to be attributed to this dilution of the toxic products and carriage of antibodies, including the so-called opsonins, to the centres of infection. In Bier's treatment, the distension of the vessels causes an exudation of lymph which bathes the tissues ; and, in Wright's method, the hypertonic saline, by its osmotic effect, produces a similar exudation. The exudates so produced also loosen and separate the tissues, and thus aid the passage of the leucocytes in their protective work. By separating inflamed surfaces, *e.g.*, the parietal and visceral layers of the pleura, they aid the healing process by preventing the formation of adhesions. Further, the fibrin, when formed, coats inflamed surfaces (Figs. 7 and 8), protects them, and tends to localise the focus of inflammation. It also brings about a temporary union between opposed surfaces, and forms a scaffolding for the processes of repair.

3. **Extravasation of Red Blood-Corpuscles.** This is not an essential phenomenon of the inflammatory process, but it is one of common occurrence. Small accumulations of red blood-corpuscles may be scattered over the inflamed area, or the exudate may be hæmorrhagic—the result of some vitamin-deficiency condition such as scurvy or a blood-disease such as leukæmia or of a widespread degeneration in the walls of the blood-vessels caused by the special action of some toxin or other irritant. The commoner condition of small foci of hæmorrhage seems to be due to the rupture of over-dilated vessels, no doubt to a certain extent aided by the alteration in, and degeneration of, the vascular endothelium. Their frequent occurrence in general septic poisonings supports the view of vascular damage being an important factor in their causation. The red blood-corpuscles appear in the form of small clumps near the engorged vessels, and are often found in the early stages of the inflammatory process. Some authorities maintain that they are carried out either between the endothelial cells, on account of

the softening of the cement-substance, or through the apertures left by the migrated leucocytes; but, though this method is possible, most evidence seems to point to rupture of small vessels as being the main means of escape.

4. **Emigration of Leucocytes.** The emigration of the leucocytes was regarded by Metchnikoff and his pupils as the essential feature of all inflammatory processes. It is certainly constant, and plays an important part. It is now generally agreed that most, if not all, varieties of leucocytes have the power of migrating from the blood-vessels, and that this migration occurs in virtue of the amœboid properties which they possess. If a transparent vascular membrane which has been irritated be observed, the leucocytes, after they have come into the peripheral stream, are seen to adhere to the walls of the vessels and then to send out pseudopodial processes, which in a short time project through the wall. The body of the cell follows, and thus the leucocytes gradually escape, and make their way through the tissues towards the noxious agent or to the site of damage (Plate I, p. 18). This passage through the vessel-wall occupies a varying amount of time, depending on the species of animal under observation, on the velocity of the blood-stream, and on other factors. It is more rapid in warm- than in cold-blooded animals, and the rapidity is greater if the blood-stream is slow. The migration is mainly through the walls of capillaries and venules, and it is specially active at the junction of tributaries (Fig. 5). It is doubtful whether the leucocytes ever migrate from arterioles. In most cases, the migration occurs from the delicate vessels composed mainly of endothelium, and the leucocytes make their way between the endothelial cells, and in this process are, no doubt, aided by the softening which has taken place in the cement-substance

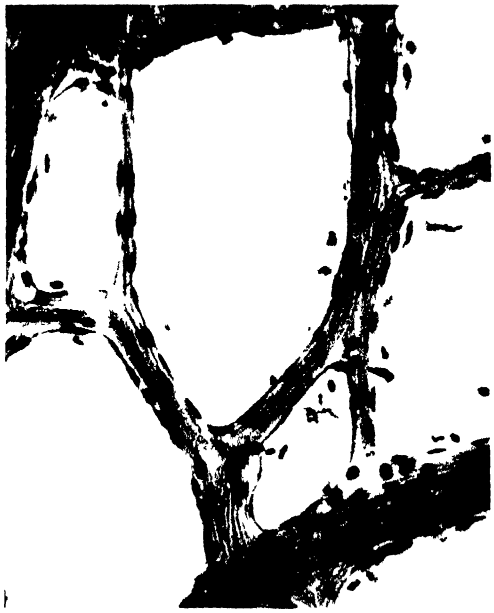

Fig. 4. Omentum of a healthy guineapig. × 200.

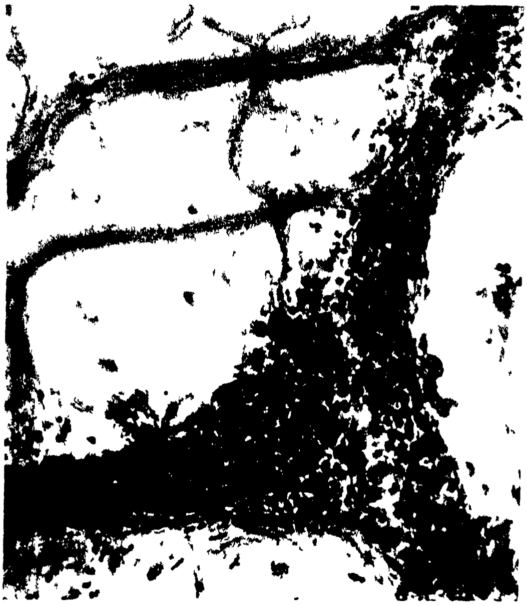

Fig. 5. Acute inflammation in a guineapig's omentum, showing emigration at junction of tributaries of venules. × 200.

there. At the same time, it is an established fact that the leucocytes can penetrate thick layers of epithelium and other tissues ; and, in their passage from some of the larger venules, which undoubtedly does take place, there must be definite migration through the fibrous and muscular walls. The time taken by the leucocytes to pass out of the capillaries and venules, as already stated, varies. In man, if the blood-flow is slow, they may escape in from eight to ten minutes ; if the flow is more rapid, they may take from one to two hours. As noted on pp. 35 and 1058, they can pass out in great numbers during surgical operations in which the electro-cautery knife or needle is employed, and within fifteen or twenty minutes there may be patches of polymorphs in and around the cauterised areas which may simulate " purulent infiltration " (Fig. 646, p. 1058).

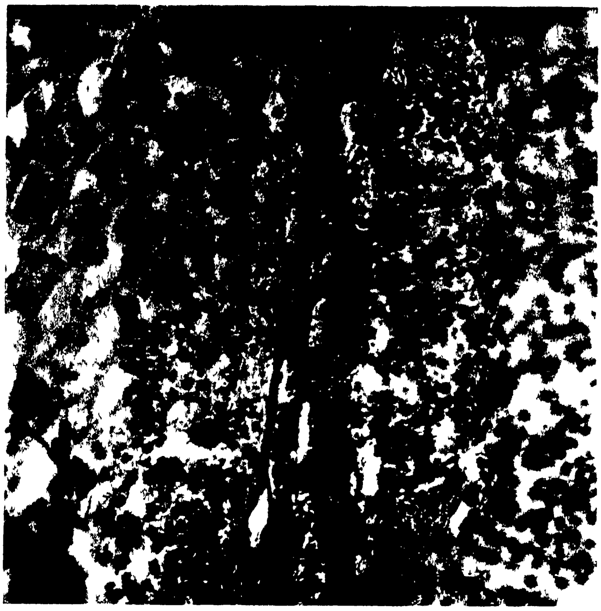

FIG. 6. Acute inflammation of omentum of a guineapig, showing a dilated vessel in the centre, filled with leucocytes, and numbers of emigrated leucocytes. × 200.

The course of the migration of a particular leucocyte is determined very largely by a positive chemotactic effect. This can be observed *in vitro* and the varying effects of masses of dead and of living bacteria and of various other foreign proteins can be determined. By making frequent observations, the paths of several leucocytes can be plotted in a given microscopical field. An index of chemotactic intensity as measured by leucocytic response can then be computed by comparing the length of the path actually travelled by a leucocyte with the straight-line distance between its original site and the foreign substance or the final position of the cell, as the case may require. (*See* Causes of Leucocyte-Emigration, p. 34.)

EXAMPLES OF ACUTE INFLAMMATION

It is convenient at this point to describe the pathological appearances seen in certain acute inflammatory diseases, with the knowledge that the essential reactions of the inflammatory process, as stated above, are dilatation of vessels, exudation of fluid from the dilated vessels, extravasation of red blood-corpuscles and emigration of leucocytes.

1. **Acute Pericarditis, Acute Pleurisy, Acute Peritonitis.**[1] As the inflammatory reaction in each of these occurs in a cavity lined by a serous membrane, it is important to remember that this serous membrane consists of a continuous layer of flattened mesothelial cells lying on a homogeneous basement-membrane and supported by subjacent layers of connective tissue with a network of fine elastic fibres near the inner surface. In health, these cavities contain a small amount of serous fluid in which are found a few free cells derived in part from the serous lining-cells. The cells are of three main types: (1) Spherical amœboid cells with a kidney-shaped nucleus and abundant cytoplasm (the macrophages or polyblasts): (2) Desquamated endothelial cells—from the serous lining: (3) Small lymphocytes.

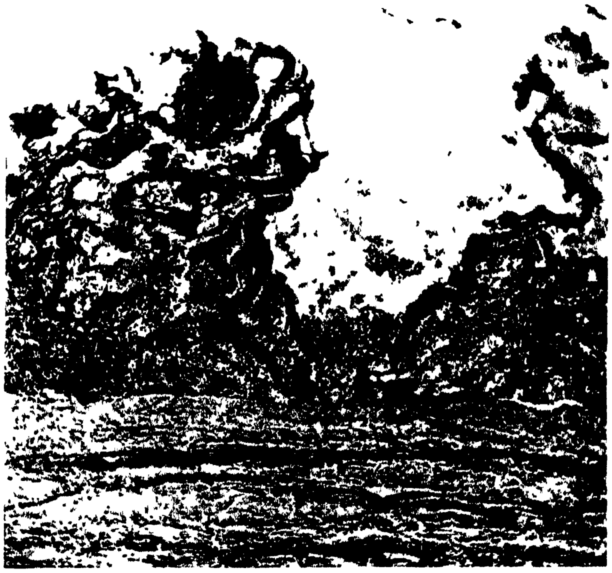

FIG. 7. Acute pericarditis, showing irregular masses of fibrin with entangled leucocytes (small dark points). × 40.

In **acute pericarditis, acute pleurisy** or **acute peritonitis,** vascular dilatation, emigration of leucocytes and exudation of lymph occur as has been described for inflammation in general. These phenomena may be confined to a localised area or may extend over the whole surface of the membrane. Fibrin-formation takes place, and, even in the early stages, on the surface of the acutely congested membrane a thin fibrinous layer is deposited. Scrapings prepared from this will show numerous leucocytes, mainly of the polymorphonuclear type, and interlacing fibrin-threads. If the exudation of lymph is scanty, a condition of "dry pericarditis" or "dry pleurisy" is produced. The inflamed and roughened surfaces are in contact, and, during the movements of the heart or lungs, friction can be detected clinically. At a later stage, adhesions between the visceral and parietal layers are formed. If, however, the fluid is greater in amount, an accumulation takes place in the affected cavity, and pericarditis, pleurisy or peritonitis with effusion is produced. The surfaces are separated from one another, adhesions are not so likely to occur, and friction is therefore not a characteristic symptom and may be entirely absent. In all cases, however, the prominent feature is the opaque layer of **fibrinous exudate** on the surface of the membranes. In addition to the fibrin and polymorphonuclear leucocytes, mononuclear cells of various types may be present in the exudate.

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[1] For further descriptions of these, *see* pp. 449–51: 532–3: and 759–60 respectively.

2. **Acute Leptomeningitis.** In its essential structure and reaction to infection, the pia-arachnoid corresponds with the serous membranes. In acute inflammation of this membrane (leptomeningitis), the reactions are identical with those described for serous membranes—dilatation of the blood-vessels, emigration of leucocytes and exudation of lymph. The thin fibrinous layer is usually well developed. The fluid, mixed and diluted with cerebrospinal fluid, may be in considerable amount in the pia-arachnoid spaces, collected at the base of the brain, in the ventricles, and, if the membranes of the cord are affected, in the spinal theca (pp. 958 *et seq.* and 981 *et seq.*, and Figs. 576–9 and 590–4 on pp. 959–62 and 979–87 respectively).

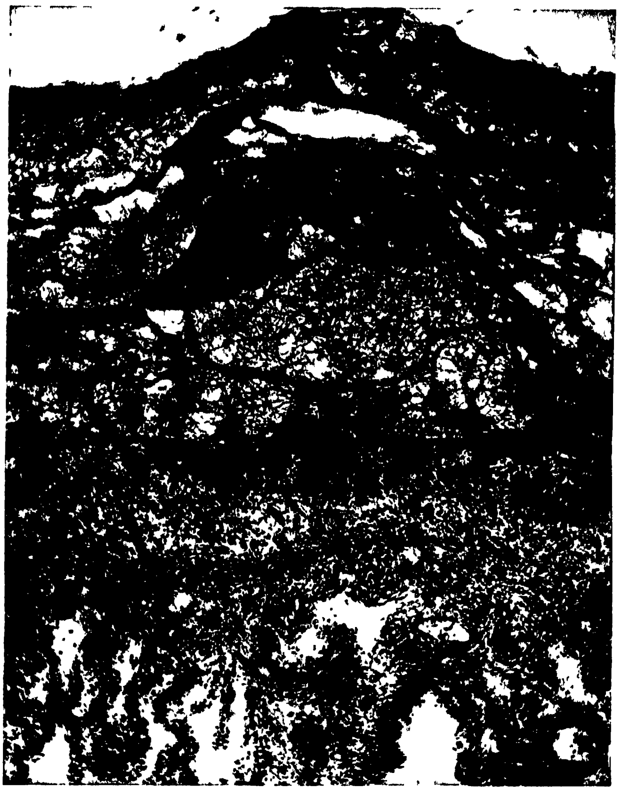

FIG. 8. Acute pleurisy, showing deposit of fibrin (fine threads and darker masses) and leucocytes on the surface of the pleura. × 60.

The fluid withdrawn from the pleural or pericardial cavities, from the peritoneal sac or from the spinal theca in acute inflammatory conditions is turbid, and this turbidity is due largely to the presence of polymorphonuclear cells. Mononuclear cells are also present. The exudate is often definitely purulent.

3. Acute Cellulitis and Abscess-Formation. If the acute inflammatory process is in the subcutaneous tissues, there may be a widespread or a localised reaction, but, in either case, any swelling is due to the accumulation of lymph and leucocytes in and between the tissues, and the redness is the result of the dilatation of the vessels. There are varying degrees of infiltration of the tissues with the inflammatory products, as well as of degenerative changes and the formation of pus. Thus a localised abscess or more diffuse suppuration is the result. Extension along the lymphatics may produce an acute lymphangitis showing as red, swollen lines representing the lymph-vessel distribution. Lymph-nodes in the path of the lymphatics may also be acutely inflamed. In the internal organs, **abscess-formation** is a common manifestation of acute inflammation.

FIG. 9. An inflammatory exudate on the surface of the heart and pericardium, the latter being turned upwards. (Acute pericarditis.)

4. Acute Bronchitis. If a bronchus in a state of acute inflammation is examined, it will show dilatation of the vessels in the vascular connective tissues and an infiltration of these tissues with polymorphonuclear leucocytes. The lymph and the leucocytes pass both towards the lumen and towards the adventitia. The basement-membrane is swollen from the imbibition of lymph, the lining epithelium shows degenerative and also proliferative changes. Much of it will be shed and will be seen in the lumen along with the leucocytes and with fibrin. The muscularis mucosæ becomes infiltrated with leucocytes and the muscle-fibres are separated from one another, swollen and sometimes partially necrotic. The infiltration may extend to the adventitia and the mucous glands show catarrhal and degenerative changes (Fig. 16, p. 40).

5. **Acute Lobar Pneumonia** (p. 527 *et seq.*). In this disease there is dilatation of the vessels in the walls of the pulmonary alveoli, accumulation of leucocytes and lymph from these vessels and the formation of fibrin in the alveoli (**red hepatisation**). In some cases a greater accumulation of leucocytes completely fills up the air-spaces and the condition of **grey hepatisation** is produced.

In all the varieties of inflammation described above, there may be small extravasations of red corpuscles or larger hæmorrhages, depending upon the degree of acuteness of the illness and the susceptibility and general condition of the patient.

From the above brief descriptions of acute inflammatory changes in certain organs and tissues, it will be apparent, that, given a knowledge of the normal anatomy and histology of a tissue or organ and of the phenomena of inflammation, it is comparatively simple to picture the pathological lesion which will result from an attack of acute inflammation in that tissue or organ.

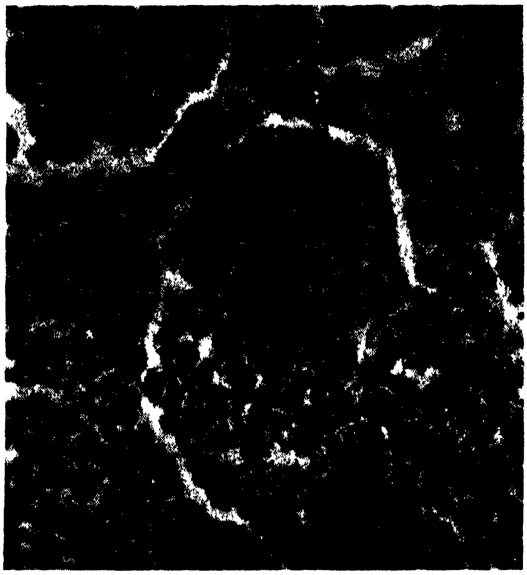

FIG. 10.—*Lung: acute lobar pneumonia in the stage of red hepatisation.* The alveolus in the centre shows congestion of the vessels in its walls; and in this air-space are fibrin and leucocytes, mainly polymorphs. × 275.

II. THE CELLS OF ACUTE INFLAMMATORY EXUDATES AND THE TISSUE-CHANGES

The facts recorded are founded on the work of Metchnikoff and his school, Councilman, Adami, Maximow, Marchand, and others, and on experimental observations made by one of the writers.[1] In these latter experiments active, cultures of *Bact. coli* and other organisms were injected into the peritoneal cavity of guineapigs, and fluid was removed by means of capillary tubes, at intervals of from five minutes up to seven days after the injection. Controls were made with normal guineapigs. Comparisons were also made with peritoneal exudates in the human subject, cases being employed in which the time of the onset of the peritonitis could be accurately determined. Many of the cells found in inflammatory exudates come from the blood, and only brief reference to their characters will be given here. Fuller descriptions will be found in the chapter on Disorders of the Blood (pp. 596 to 601).

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[1] "The Cells of Inflammatory Exudations: An Experimental Research as to their Function and Destiny, and also as to the Origin of the Mononucleated Cells": by J. M. Beattie, *Jour. Path. and Bact.*, 1903, **8**, 129. Many of the times and periods stated in this chapter for the various phases and processes of inflammation and repair refer to the experimental work described in this particular paper. These times and periods will naturally vary with factors such as the site and nature of the injury or wound, the tissues involved, and the age, nutrition and state of health of the patient. In this connection, our readers will find much of interest in Alexis Carrel's book, "Man, the Unknown," which deals with the problems of cell-life and the interdependence of man's bodily and mental activities at different age-periods, as well as the adaptivity of these processes to the changing conditions of his environment.

1. **Polymorphonuclear Leucocytes** (*cf.* pp. 598 and 985–7). These leucocytes are, in health, the most numerous variety in the blood, where they constitute about 60 to 70 per cent. of the total leucocytes. The nucleus is divided into segments or lobes. The cytoplasm contains irregularly scattered fine granules, which stain faintly with both acid and basic dyes. These leucocytes are numerous in an inflammatory exudate about three hours after inoculation, and they become more abundant in from eighteen to twenty-four hours (Plate III, p. 30, Fig. 1). If they are able to overcome the irritant, they begin to diminish in from thirty-six to forty-eight hours (Plate III, p. 30, Fig. 2), and this diminution is marked in from sixty to seventy-two hours. In from eighty-four to one hundred and fifty hours they may have disappeared from the exudate. If, however, they are not able to overcome the irritant, a progressive increase takes place ; and it may be said that the polymorphonuclear leucocytes will continue to migrate in enormous numbers as long as the need for defence exists, and as long as the strain of increased production can be borne by the blood-forming tissues—in this case, the bone-marrow. In all of our experiments where the injection produced a fatal result, these leucocytes were always in enormous numbers, even in cases where death was delayed as long as ninety-six hours. These results apply to almost all forms of inflammation. With certain organisms, *e.g.*, the tubercle bacillus, however, in the early stages the exudate contains mainly mononuclear cells, to which reference is made later, the polymorphonuclear response being relatively unimportant.

2. **Coarsely Granular Eosinophils or Oxyphils** (*cf.* p. 599). From 1 to 4 per cent.[1] of the white corpuscles of blood, in people apparently healthy, show, when stained with eosin, brilliantly coloured pink granules in their cytoplasm. These are larger and more highly refractile than the much smaller granules of the polymorphonuclear leucocytes. The lobed character of the nucleus is not so pronounced, and it stains less intensely with the basic dyes. These cells are fragile, and readily break down, with scattering of their granules. In the experimental work to which reference has been made, these leucocytes were found only in small numbers in inflammatory exudates ; but in certain conditions, and especially those associated with hypersensitive states (anaphylaxis, allergy, atopy, pp. 135 to 137), they may be increased in the blood and appear in considerable numbers in the exudates, and may act on the tissues in virtue of the ferments or hormones which they are supposed to elaborate. Their numbers may be increased in the blood of guineapigs by repeated injections of foreign proteins. In the human subject, they are present in the blood in considerable numbers in infections due to certain animal parasites (especially various worms) ; they are increased in the blood and tissues in some diseases of the skin, and in

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[1] But with regard to the " normal " number of eosinophils in the blood, *see* p. 599.

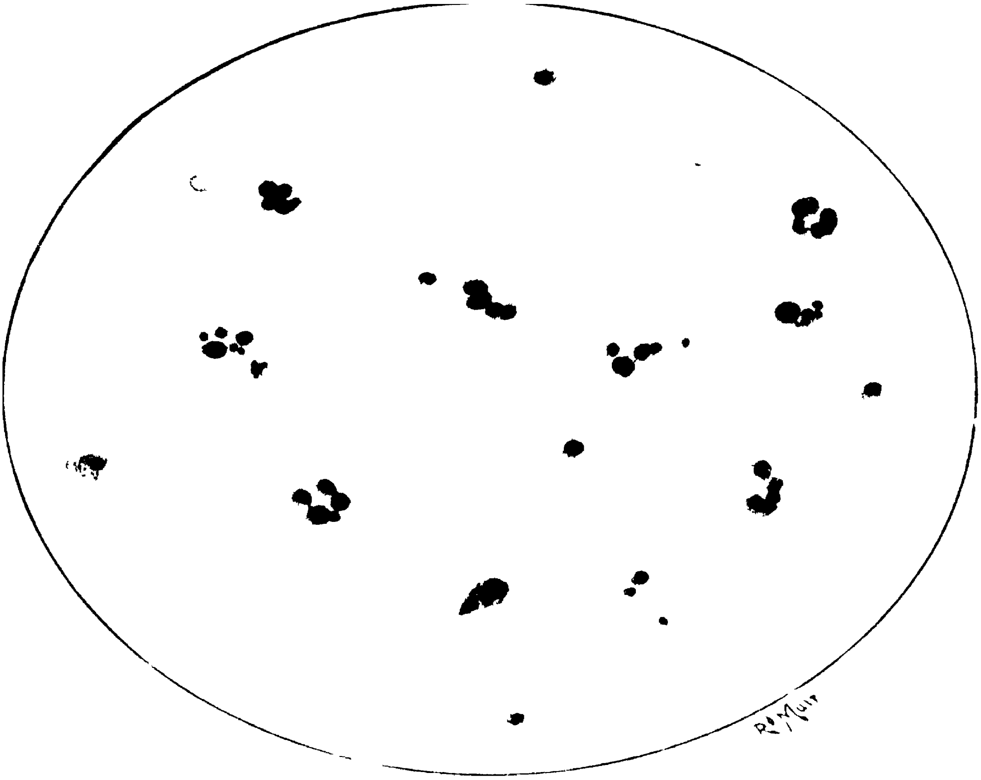
DESCRIPTION OF PLATE II

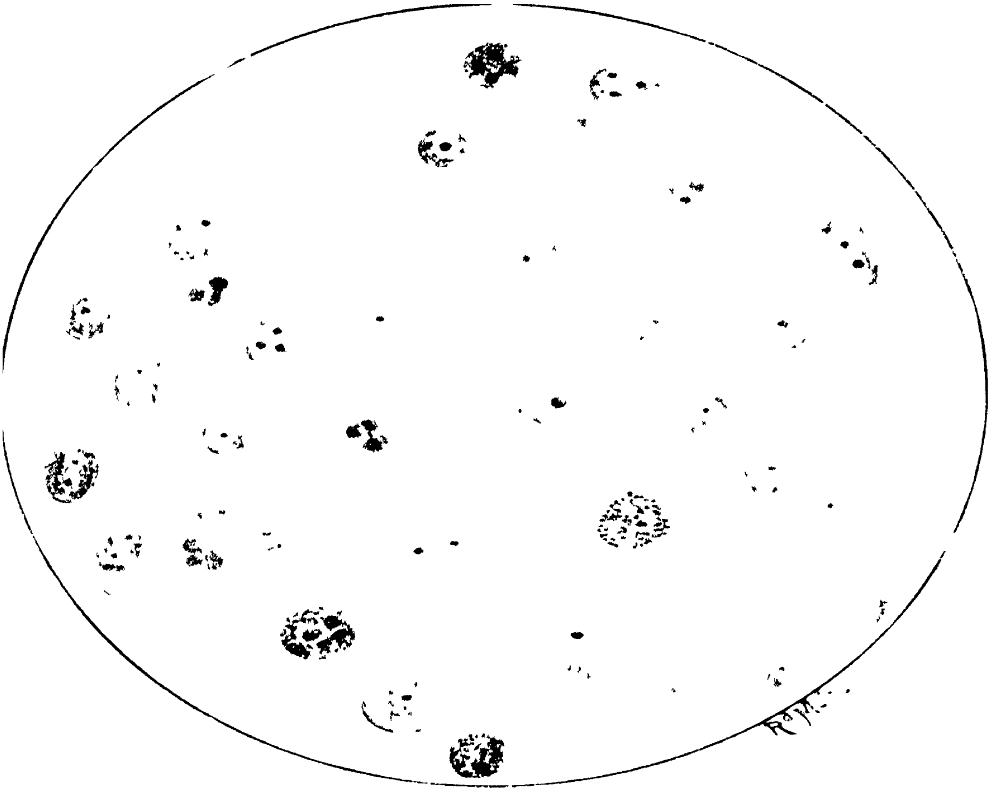
PLATE II

Fig. 1. *Peritoneal Exudate*, six hours after intraperitoneal injection of *Bacterium coli*. Shows fragmentation of nuclei and separation of portions of the protoplasm with the nuclear fragments. Wet film stained with eosin and methylene blue. × 1000

Fig. 2. *Peritoneal Exudate*, twenty-three hours after intraperitoneal injection of typhoid bacilli. Note the great proportion of mononucleated cells, which are actively phagocytic and amœboid. These cells are probably endothelial in origin. Wet film stained with eosin and methylene blue. × 1000

PLATE II. p





asthma, in which disease they may be present in large numbers in the sputum. Ulcers of the stomach and intestines may show many eosinophils in their floors; and these cells occur in the exudate and in the walls of inflamed uterine (Fallopian) tubes, in the vermiform appendix and, in considerable numbers, in the lymph-nodes in lymphadenoma (p. 681).

Basiphils (*cf.* pp. 163, 599 and 623), about one-half per cent. of the white cells in the blood are characterised by the presence of irregularly scattered larger and smaller basiphil granules, or granules which show metachromatic staining. For their distribution in and around the walls of blood-vessels and their *rôle* in the production of **heparin,** *see* Fig. 360A, p. 599: and p. 163. Apart from this function, there is no evidence that they take any active part in the processes of inflammation.

3. **The Mononucleated Cells.** These may be divided thus:—

(*a*) **Lymphocytes** (*cf.* pp. 600 and 985–7). The majority of these, regarded by most hæmatologists as the mature or adult members of the lymphocyte-group, are **small cells** with a relatively large darkly-staining nucleus, which is spherical or sometimes shows a slight indentation at one side. The cytoplasm is relatively scanty—often merely a narrow rim round the nucleus—and may contain a few small scattered purplish-red or azur-staining granules which have no affinity for oxydase stains. The **larger lymphocytes** are cells similar to these, but larger in size and having more abundant cytoplasm and paler nucleus. All **intermediate sizes** between these larger and the more numerous small lymphocytes are found, and recent observations confirm the view that the latter are motile (p. 600). The cells of this lymphocyte-group constitute, in the adult, about 25 to 35 per cent. of the white cells of the blood, but are often relatively more numerous in children (p. 600).

(*b*) **Monocytes** (*cf.* p. 600A). These are large, mononucleated, amœboid cells with abundant cytoplasm and a nucleus which may appear rounded, ovoid or kidney-shaped, or even horseshoe-shaped. The nucleus stains less intensely than that of the small lymphocytes, the chromatin-granules being finer and the nuclear membrane thinner. These cells are present in small numbers (3 to 6 per cent.). In an ordinary dried stained blood-film it is often impossible to distinguish between the large lymphocyte and various types of the monocyte—in fact, types may be seen which may be regarded as transitional forms.

Under this term "monocyte" are included the large mononuclear cells, the hyaline and the endothelial leucocytes, the histiocytes, clasmatocytes and macrophages of various writers. The origin of the monocytes is a much debated problem. Some authors hold that they are formed in the bone-marrow, others that they are developed by proliferation of the lining-endothelium of the blood-vessels (endothelial leucocytes); but the two main views at present held are (1) that they arise from the fixed and wandering histiocytes (p. 30), including endothelial cells, in various parts of the body: or (2) that they are formed by progressive development from the small lymphocyte—a view with which most physiologists and pathologists do *not* agree. The former is the generally accepted view (*see also* pp. 600A, 961 and 985 *et seq.*).

In inflammatory exudates produced experimentally, various kinds of mononuclear cells are seen in three hours after inoculation, but, for the first twelve hours, they are scanty. In from eighteen to twenty-four hours the number becomes greater, and this increase continues *pari passu* with the diminution of the polymorphonuclear leucocytes, until, after the lapse of from fifty-four to eighty-four hours, most of the cells present are of the large mononuclear type. This increase is maintained until one hundred and fifty hours or longer (*cf.* Figs. 577–8, pp. 960–1 : and Figs. 592–4, pp. 985–7).

Origin and Function of the Various Cells found in Inflammatory Exudates

1. **The polymorphonuclear leucocytes** come from the bone-marrow by way of the blood and have as their main function the destruction of the irritant. They appear very early in the process of inflammation (Plate II, p. 26, Fig. 1), ingest irritant particles, and ingest and digest organised irritants, *e.g.*, bacteria (Plates II, III, IV, opposite pp. 26, 30, 32). Inert material such as carmine or vermilion is taken up by these cells soon after it is injected. Bacteria are also ingested in a short time, but, in the experiments referred to above, the ingestion of motile bacteria was a much later phenomenon than the ingestion of particles of carmine. This suggests that the bacteria are injured before the cells are able to seize upon them. Metchnikoff maintained that the cells can ingest uninjured living bacteria, but most observers hold that the organisms are first altered by substances contained in the plasma. Our observations suggest that, as a result of the inflammatory reaction, the plasma acquires new properties which enable it to injure or destroy bacteria, body-cells, etc. It seems reasonable to suppose that the migratory and proliferated cells, which are found at the inflammatory focus, have at all events a share in the local production of these bacteriolytic, cytolytic, or other substances.

2. **The eosinophil leucocytes** are, we believe, phagocytic to bacteria, though only to a minor degree and much less actively than the polymorphs ; and, in response to certain chemotactic stimuli, they may, as Ehrlich held, to some extent take the place of the polymorphonuclear leucocytes and perform similar functions.

3. **The lymphocytes.** The reaction of these cells in inflammatory conditions is uncertain, but their function in the acute process is probably relatively unimportant. Some authors hold that, in the chronic conditions and in those in which the cell-reactions are delayed for some days, such as infections with the spirochæte of syphilis and the tubercle bacillus, or where toxins have been acting over a fairly long period, as in the kidney in prolonged cases of scarlet fever, in subacute inflammation of the kidney, in cirrhosis of the liver, etc., these cells migrate in considerable numbers from the blood-vessels. It is true that, in such conditions, collections of " small round cells," resembling lymphocytes, are seen in the tissues. They are also present at even a comparatively early stage in the cerebrospinal fluid in cases of mumps, " lymphocytic choriomeningitis," measles, encephalitis, poliomyelitis and other infectious diseases, but are a more pronounced feature in chronic conditions, *e.g.*, general paresis and other forms of syphilis. In the perivascular lymph-spaces they form the " cuff-cells " in the brain in epidemic encephalitis (Figs. 58 and 59, pp. 111–12). Maximow emphasised the importance in inflammation of the amœboid wandering cells present in loose connective tissue. The smallest of these are indistinguishable from the lymphocytes of the blood, the larger are the

monocytes. He stated that these small lymphoid cells have not necessarily emigrated from the blood-vessels, because similar cells originate in the embryonic mesenchyme and may remain at the site of production. He held, however, that, during the process of inflammation, lymphocytes do migrate from the blood-vessels and may become large phagocytes, a view which is at variance with that of most cytologists and hæmatologists. During the first two days these cells can be distinguished from those originating in the mesenchyme—the polyblasts (p. 31)—by their smaller size, but, after this period, they cannot be differentiated. Though we agree that the blood-lymphocytes can and do migrate into the tissues, we can also corroborate the view of Adami and others, that the lymphocyte-like cells seen in the tissues and exudates during the inflammatory process are derived largely by proliferation from the lymphoid cells normally present in various situations, but especially in the perivascular tissues. These lymphocyte-like cells also undoubtedly migrate from the lymph-nodes and from the lymphatic vessels. In the later stages of inflammation, transitions between cells resembling, if not identical with, the larger lymphoid cells and the large macrophages, can be seen (Plate III, opposite p. 30, Fig. 2, and Plate IV, opposite p. 32, Fig. 2), and Cappell is of opinion that his experiments (1930) " show that cells indistinguishable from lymphocytes, when free in an inflammatory exudate, may undergo a series of progressive changes culminating in their transference into macrophages, and during these changes they may pass through a stage in which they present the morphological appearances and the supravital staining-reactions of monocytes." [1]

Fig. 11. Lymphocyte-like cells from a chronic inflammatory focus. × 1,000.

4. **Plasma-Cells** (Fig. 15, p. 39). These cells occur in groups or masses, are seen especially in syphilitic lesions, and are present often in considerable numbers in granulation-tissue and in healing wounds, as well as in the cerebrospinal and other inflammatory fluids and in the tissues, in certain acute, subacute and chronic inflammatory lesions. Plasma-cells are usually somewhat larger than lymphocytes—the nucleus is eccentrically placed, has a coarse chromatic network with the so-called cart-wheel or clock-face arrangement of its particles, and, in the stained cell, is surrounded by a pale halo. The cytoplasm is strongly basiphilic and may show vacuolation. They are feebly amœboid and it is doubtful whether they possess any phagocytic properties. They do not seem to change into any other cell-type, though most authors agree that they are formed from the lymphocytes. Their function is unknown.

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[1] But in this connection *see* pp. 31, 600 and 600A, 961 and 985–988, and the opinion there expressed that the smaller cells are the mature forms derived *from* the larger mononuclear cells or large lymphocytes.

5. **Monocytes, Histiocytes, Macrophages, Large Mononuclear Cells, Reticulo-endothelial Cells.** It is extremely difficult to differentiate cells which have been classed under the above names, and it is now usual to group them all under the one term, **reticulo-endothelial cells.** Their common characteristic is that they are phagocytic and that they all store up colloidal dyes after intra-vital staining. The origins of certain of these cells and some of their functions may be entirely different from one another, so that there is no real anatomical or physiological significance in the name. Maximow considered it unsuitable and incorrect because it referred to only one representative of the group—the reticular cell—while a large proportion of the endothelial cells—those lining the blood-vessels—are not members of the group. He preferred the term histiocyte. The term " reticulo-endothelial," as applied to these cells, is, however, in common use and is convenient. Microglial cells as members of this group are described on pp. 955–6, 1055–6 and 1159–61. According to Maximow and Bloom [1] (1933), in the connective tissues throughout the body, there is a group of cells fixed or free, which, as we have just said, act as phagocytes and can invariably store dyes and other colloidal substances. These, they say, are "the histiocytes or resting wandering cells." These cells, as seen in stained films, are irregular, rounded, ovoid or spindle-shaped, sometimes with branching processes. The nucleus is ovoid or kidney-shaped. A study of the cells during life, either on a warm stage or by the "speeded-up " slow-motion films of Canti, shows that the shape and size, both of the cells and of their nuclei, are constantly altering.

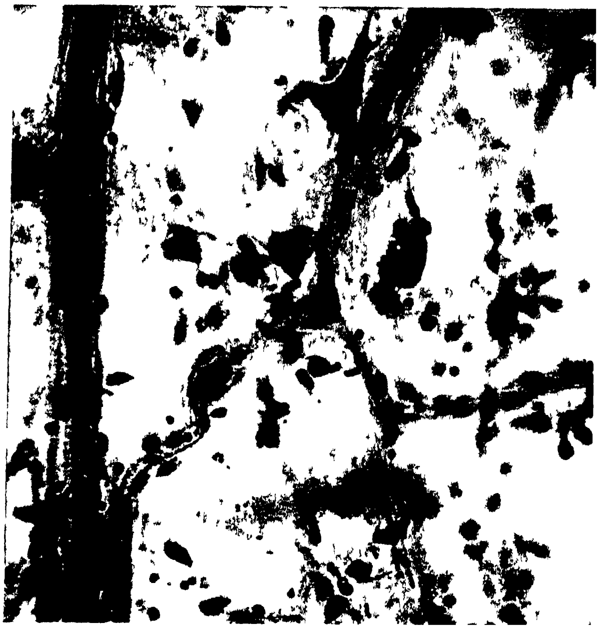

FIG. 12. Omentum from a case of peritonitis following rupture of the liver. Death in three days. Cells are mainly mononuclear in type, and some have branching processes. These correspond with histiocytes. × 200.

In addition to the members of the reticulo-endothelial system, there are

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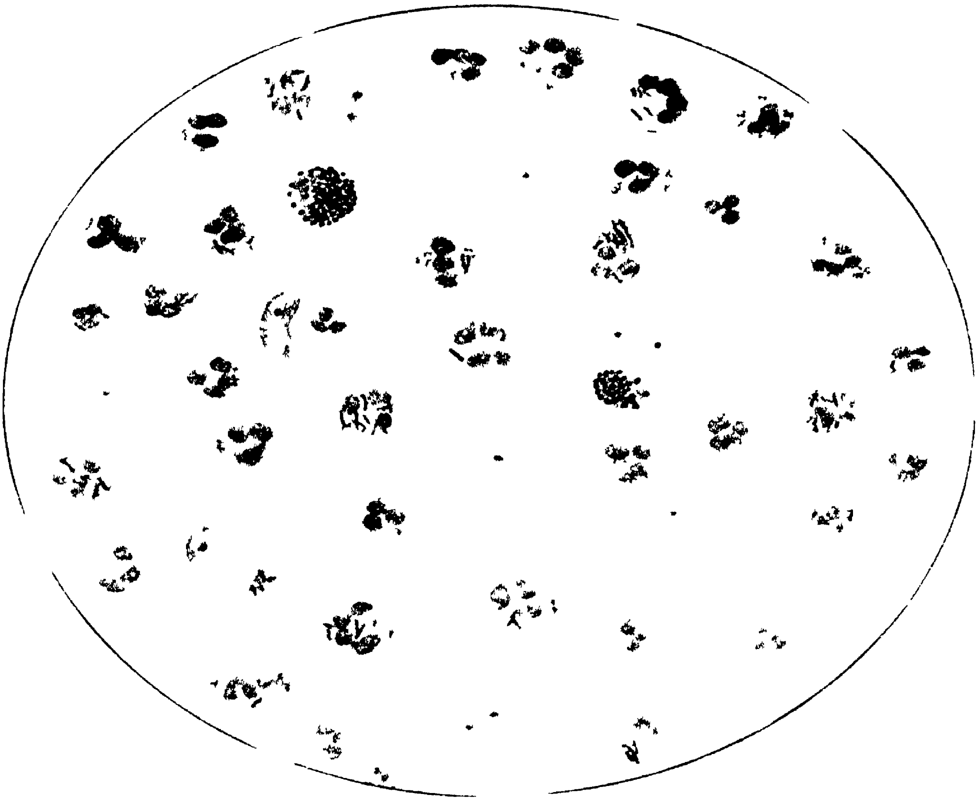
[1] " Textbook of Histology," by A. A. Maximow, completed and edited by William Bloom, Chicago, 3rd edition, 1938 : W. B. Saunders Co. Ltd., London (first edition published in 1933).

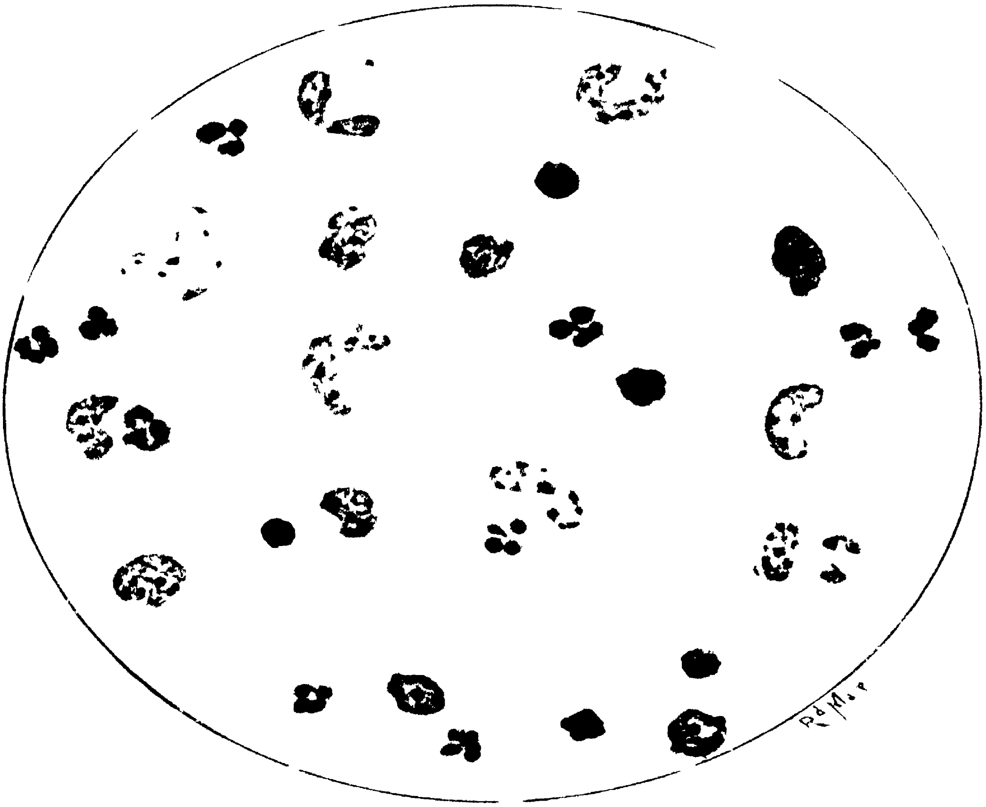
DESCRIPTION OF PLATE III

PLATE III

Fig. 1. *Peritoneal Exudate,* twenty-four hours after intraperitoneal injection of *Bacterium coli.* Shows relative proportion of polymorphonuclear leucocytes to mononucleated cells, and active phagocytosis. Note the pseudopodia of the mononucleated cells. Wet film stained with eosin and methylene blue. × 1000

Fig. 2. *Peritoneal Exudate,* forty-eight hours after intraperitoneal injection of *Bacterium coli.* Shows phagocytosis and transition stages between the large and the small mononuclears. Wet film stained with eosin and methylene blue. × 1000





cells with similar functions in the lymphoid and myeloid tissues and in the spleen-pulp—the reticular cells : in the liver, the " Kupffer-cells " : and lining-cells of the sinuses in the spleen, suprarenals, hypophysis, etc.

During the inflammatory reaction, all these reticulo-endothelial cells or histiocytes, fixed and resting, may become transformed into large amœboid, wandering, phagocytic cells and are found in large numbers in the exudates and, in vitally-stained animals, are seen filled with the dye.

They are the **macrophages** of Metchnikoff and the **polyblasts** of Maximow. Their essential function is the removal of damaged or dead cells, bacteria and other foreign material from the tissues. In exudates, the variations in size, shape and staining properties are considerable, and this is no doubt dependent on the stage of their development and degree of activity (Plates III, IV, V and XI, opposite pp. 30, 32, 34, 222). Working with fixed and stained films, there is a tendency to regard these variations as indicating different types of cells, whereas, when the cells are studied in their living condition, it is obvious that many of these apparent variations are due merely to transitions in shape or size resulting from growth or alterations in functional activity.

As we have already indicated, the macrophages may be derived from cells which are indistinguishable from the larger lymphocytes, and we agree with Cappell (1930) who, from his experimental work, states that "no clear distinction can be made by supra-vital staining between lymphocytes, monocytes (the mononuclear cells of the blood and tissues) and macrophages ; whilst typical examples of each can be readily identified, the three types are connected by all intermediate stages." Cappell also believes " that a progressive development is going on in the smaller cells, by which they are rapidly acquiring the functional character of young macrophages."[1]

6. **Fibroblasts and Fibrocytes.** In the embryo, the fixed stellate cells of the mesenchyme remain as undifferentiated embryonic cells or are converted into fibroblasts. The undifferentiated forms may become wandering cells and then be converted into other cell-types—histiocytes, macrophages, etc. The fibroblasts proliferate abundantly, do not give rise to other types of free cells. Under ordinary circumstances, they are *not* phagocytic ; and are concerned mainly in building up new tissue. These are discussed under Repair, p. 42, and *see also* Fig. 579, p. 962.

7. **Endothelial Cells.** Most authors regard the endothelium lining blood-vessels and lymphatics as a " fixed tissue," but Mallory and others maintain that some of the mononuclear cells of the blood are derived from this endothelium. In inflammation and by tissue-culture experiments, such endothelial cells are often found swollen, and sometimes mitotic figures are observed in them ; and they may become free wandering cells (Plate XVII, p. 616 : and Fig. 578, p. 961).

NOTE. The part played by the fixed cells is disputed, but there is no doubt that some of these, *e.g.*, the endothelial cells lining serous membranes, react to the irritant in the very earliest stages of the inflammatory process. They become phagocytic, they are freed from the surface and according to some authorities they proliferate and produce types of wandering cells which are found in the exudate (Plates III, IV and V, opposite pp. 30, 32 and 34 and Figs. 578 and 592–4, pp. 961 and 985–7).

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[1] The views of one of the authors (W.E.C.D.) are *not* in accord with those of Cappell, expressed above, that small lymphocytes grow up into large monocytes. *See* pp. 960–961 and 985–987, and the microphotographs illustrating them.

The mesothelium of serous cavities, *e.g.*, pleura, pericardium, peritoneum, etc., is shed, often in masses or sheets, during the inflammatory process (Plate IV, Fig. 1). The cells are found free in the exudate, many of them containing foreign particles and remains of other cells. They present all the characteristic appearances of macrophages and are actively phagocytic.

8. **Giant-Cells.** Some of these are formed by aberrant cell-growth, where the nuclei undergo division without the cytoplasm following suit; but many of them are formed by fusion into plasmodial masses of endothelial, and perhaps of other forms of mesoblastic, cells. They are amœboid, and actively phagocytic. They may be found early in the acute stage of the inflammatory process, but, more commonly, at a later period. They are generally well developed where resistant tissues, *e.g.*, bone, or foreign bodies such as catgut, etc., have to be absorbed (Fig. 24, p. 48), and they are a special feature of certain chronic inflammatory diseases (Fig. 32, p. 60), *e.g.*, tuberculosis or syphilis.

PHAGOCYTOSIS

(*See* Coloured Plates I and XI, facing pp. 18 and 222, and II, III, IV, V, facing pp. 26, 30, 32 and 34.)

Various references have already been made to the ingestion of bacteria, foreign particles, red blood-corpuscles and other cells by the leucocytes, but the subject is of such importance that special consideration of it is necessary. The brilliant work of Metchnikoff and his pupils has given to the subject of phagocytosis an extremely prominent place, not only in the study of the processes of inflammation, but in the much wider sphere of immunity against disease. We may not agree with all his conclusions, but about the accuracy of his observations there can be no doubt. They have stood the test of time, and, in spite of all opposition, are now almost universally accepted. Metchnikoff studied the subject in numerous types of the animal kingdom and showed that phagocytosis is an almost universal endowment of cell-life, that it is the most important defensive agency against disease or disease-producing products, and that it is an essential factor for the carrying on of cell-life. Much of the moulding of the body-tissues (*e.g.*, the bones) is performed by phagocytic cells; waste-products, effete cells and damaged tissues are removed by them; and they are the producers of secretions of various kinds which play important parts in protection against, and in the cure of, disease. Though phagocytosis, as stated above, is an almost universal endowment of animal cell-life, some types of cell, owing to differentiation and specialisation of function, have in whole or in part lost this property. Thus, under ordinary conditions, the fibrocytes as noted on p. 31, and the nerve-cells are not phagocytic, but Cappell has shown that even the fully differentiated fibrocyte can take up certain dyes. Abnormal cells, *e.g.*, tumour-cells (p. 271), may be actively phagocytic. There is general agreement, however, that under normal conditions the main phagocytes are the leucocytes of the blood and the fixed and wandering tissue-cells—histiocytes and reticulo-endothelial cells. Some writers maintain that the liver- and kidney-cells sometimes exhibit definite phagocytic action.

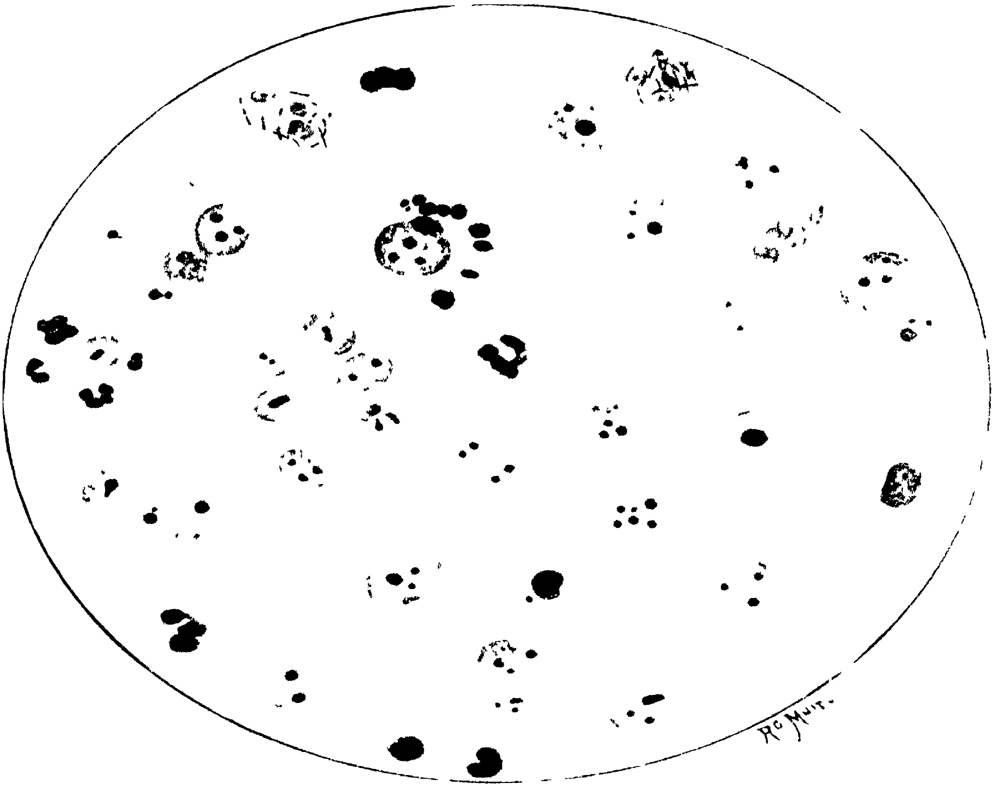
DESCRIPTION OF PLATE IV

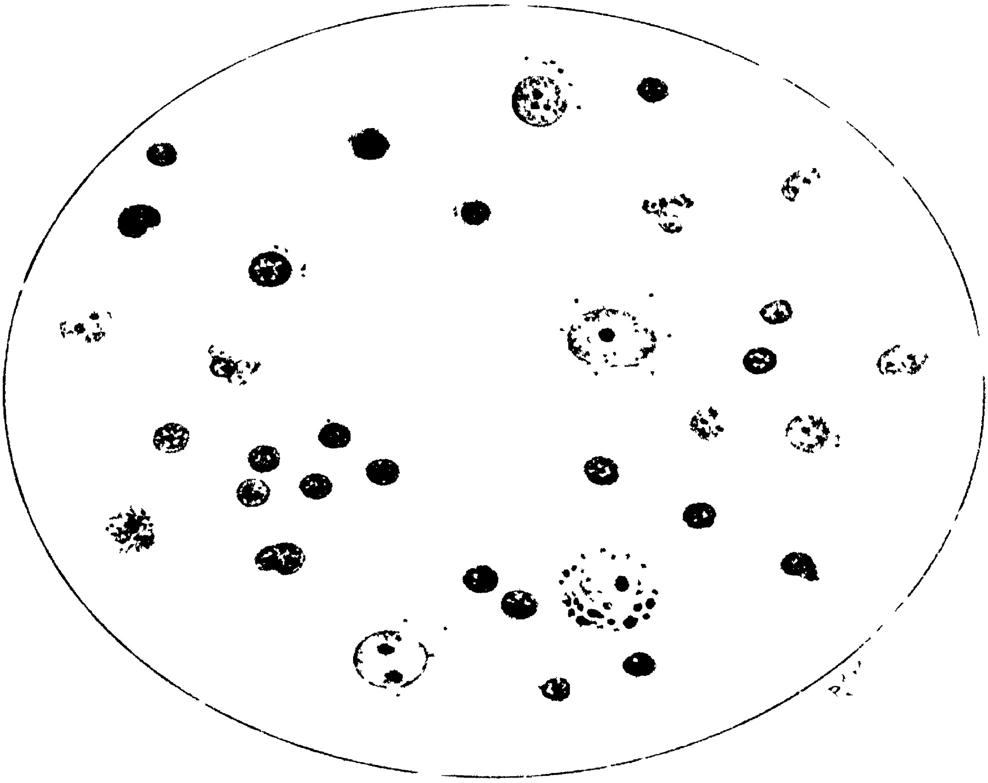
PLATE IV

FIG. 1. *Pleural Exudate* (from a case of acute pleurisy). Shows phagocytosis by polymorphonuclear leucocytes, also vacuolation of, and phagocytosis by, the endothelial cells. Wet film fixed with Muir's solution (tannic acid and corrosive-sublimate) and stained with eosin and methylene blue. × 1000

FIG. 2. *Pleural Exudate* (same case at later period). Shows increase in mononuclear cells as compared with polymorphonuclear leucocytes, and transition-stages between the large and the small mononuclears. Wet film fixed with Muir's solution (tannic acid and corrosive-sublimate) and stained with eosin and methylene blue. × 1000

PLATE IV p





In the processes of inflammation, the phagocytic properties of the cells become more pronounced. In the early stages, the migratory cells which are the first to show active phagocytosis are the polymorphonuclear leucocytes; but the fixed endothelial cells, while still in position on the surface of an inflamed serous membrane, may be actively phagocytic even before the leucocytes have migrated.

The polymorphonuclear leucocytes are concerned in the phagocytosis especially of bacteria, but they may also ingest red blood-corpuscles, particles of dead or necrosing tissues, and foreign bodies such as particles of carbon, and blood-pigment (Plate III, Fig. 1, p. 30). **Living** bacteria are undoubtedly taken up by them, and the process of digestion may be very incomplete—so incomplete indeed that after some time the bacteria may still be capable of growth in suitable culture-media. The polymorphs frequently simply carry their ingested material to the surface, *e.g.*, of an ulcer, or into the lymphatic channels and lymph-nodes, where they may deposit it. These polymorphs have been termed **microphages** by Metchnikoff, to distinguish them from the larger mononucleated phagocytes, the **macrophages,** which have the principal share in the removal of dead or degenerated material. Within the macrophages a clear space containing fluid surrounds the ingested material, and, in these spaces, which may be numerous (Plate V, Fig. 2, p. 34), there is a gradual disappearance or digestion of the included bacteria, and of the polymorphonuclear leucocytes or other englobed cells. The nuclei of the included cells become fragmented, and gradual solution or digestion of the chromatin and disappearance of the cytoplasm take place. The red corpuscles shrink, and their hæmoglobin may either be absorbed or may remain as pigment within the phagocyte. In some cases, and especially with certain bacteria—*e.g.*, tubercle bacilli (Plate V, Fig. 1,

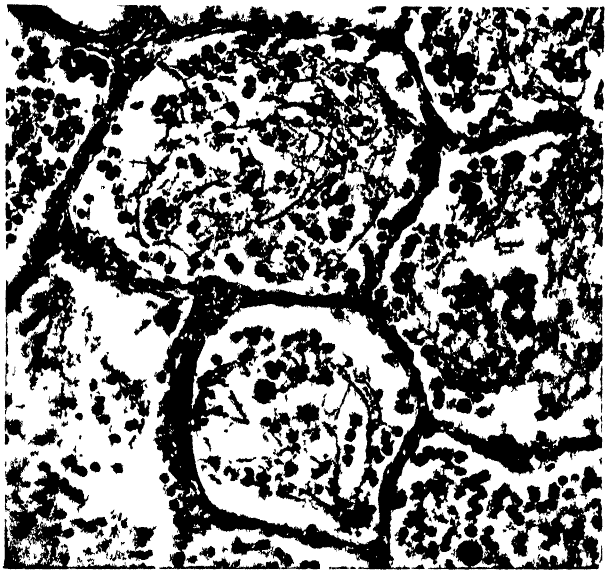


FIG. 13. Acute Pneumonia, showing fibrin and leucocytes in the air-spaces of the lung. × 200.

opposite), the bacilli of leprosy and glanders, meningococci and gonococci—the organisms may remain in the cells for a long time with little or no destructive changes taking place in them, and it would appear that they are even capable of proliferating actively. In this respect they resemble some of the parasites infesting unicellular organisms. The amount of phagocytosis appears to be in inverse proportion to the degree of virulence possessed by the particular micro-organism concerned. The phagocytic action is aided, as has been stated previously, by substances in the blood-plasma and lymph which have an injurious action on living organisms. These agglutinins, opsonins, etc., are in all probability produced by the various cells of the body—not specially or exclusively by the leucocytes.

Fate of the Various Cells in the Absorption of the Exudate and in Repair. Many of the polymorphs are cast off or destroyed as pus-cells, others are ingested by the mononucleated phagocytes, whilst some enter the lymphatics and possibly also the blood-stream. They take no direct share in the formation of new tissue. The mononucleated cells may migrate into the lymphatics and pass to the lymph-nodes or enter the blood-stream and be carried to the spleen, bone-marrow, and various other organs and tissues, where their contents are deposited, and where the cells undergo disintegration.

Causes of Leucocyte-Emigration. We have seen that the polymorphonuclear leucocytes are actively amœboid, and that, when the blood-stream is slowed, they pass to the periphery and attach themselves to the walls of the vessels. Protoplasmic processes are projected through the vessel-wall, the nucleus with a small ring of cytoplasm being the first part of the cell to pass out. Finally, the whole cell is seen to escape and to migrate to the definite site of irritation. As a result of the inflammatory process, the endothelium of the dilated vessels becomes swollen, and the cement-substance between the cells loosened. The swelling of the endothelium, the slowing of the stream, and the dilatation of the vessels must aid the accumulation of the leucocytes at the periphery. The loosening of the cement-substance renders the walls of the capillaries more pervious, and thus makes the passage of the leucocytes easier ; but the essential point in this emigration is the active amœboid power of the leucocyte itself. This emigration is determined by some attractive force outside the vessel. It has been proved by experiment that certain products of bacterial activity and tissue-metabolism, as well as certain chemical and physical agents, attract wandering cells, whilst others have no attractive power. Leber (1891) studied this subject by introducing glass tubes, closed at the outer end and containing chemicals, into the blood-vessels. He and other observers found that certain chemical substances, *e.g.*, various compounds of mercury, finely-powdered copper, turpentine and other chemicals, exert a positive attraction : whilst quinine, chloroform, glycerol and alcohol act negatively, *i.e.*, repel the leucocytes : that dilute solutions sometimes act positively, whilst those more concentrated have a negative action. The products of growth of most of the pyogenic bacteria and the toxin of diphtheria bacilli, if not too concentrated, attract leucocytes in great numbers, whereas, if they are concentrated, the leucocyte-emigration is not marked. The substance "leukotaxine," described by Menkin as formed in inflammatory exudates,

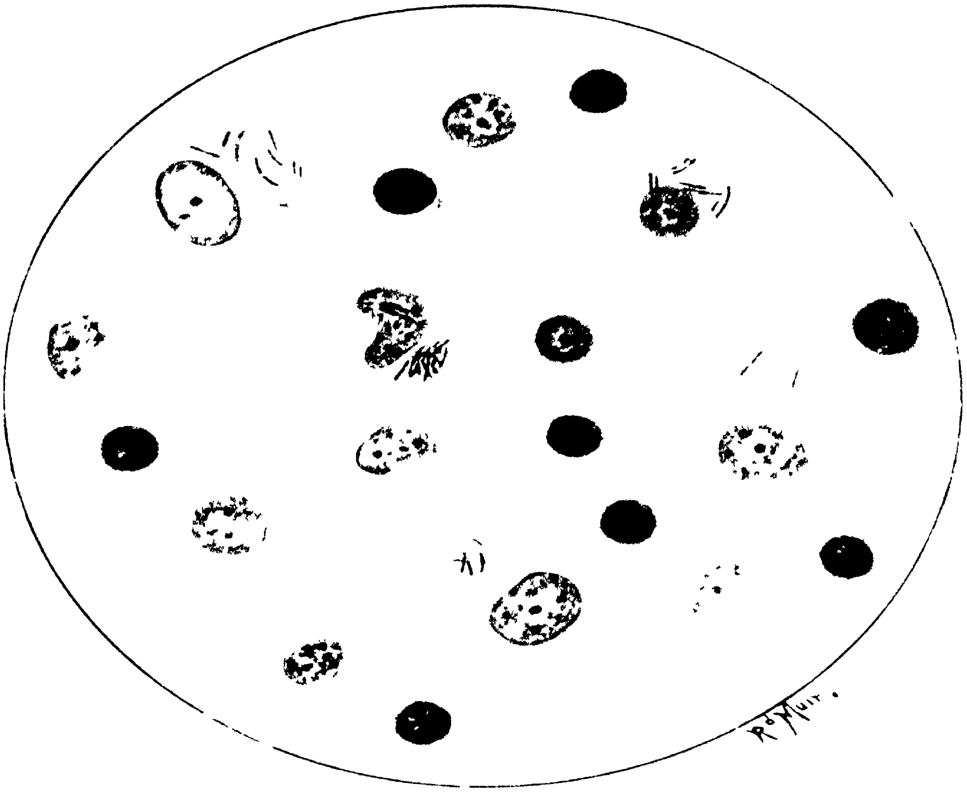
DESCRIPTION OF PLATE V

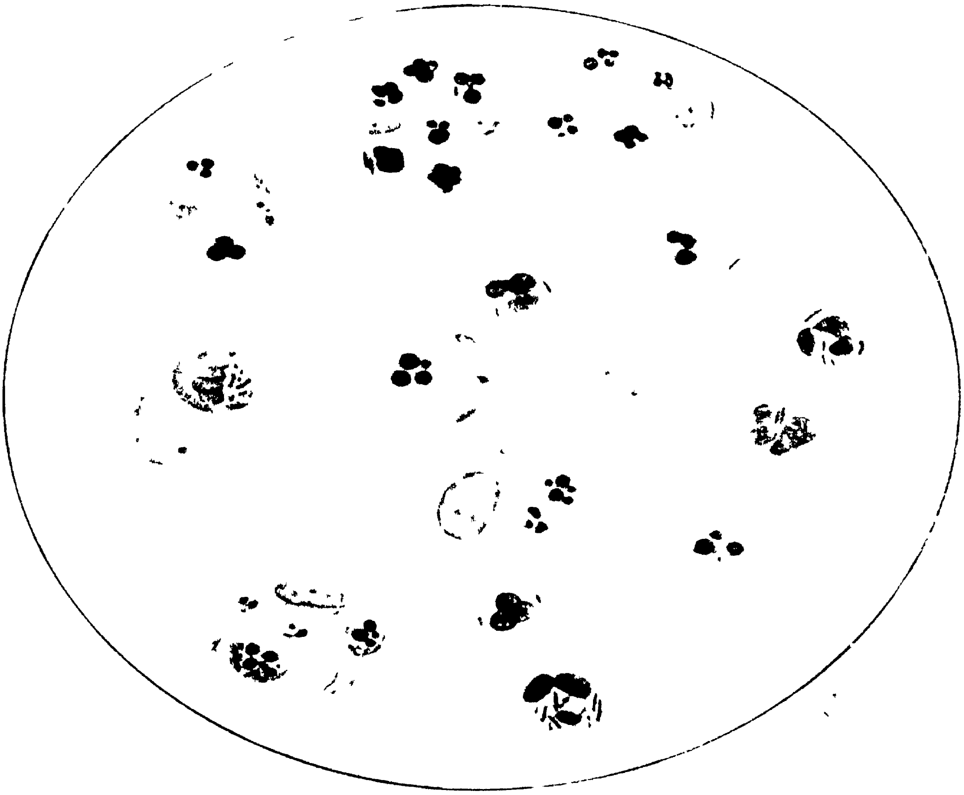
PLATE V

FIG. 1. *Peritoneal Exudate*, twenty-five days after intraperitoneal injection of tubercle bacilli. Shows transition-stages between the large and the small mononuclears, the phagocytosis of both cells and bacilli, and the absence of polymorphonuclear leucocytes. Film stained by Ziehl-Neelsen's method. × 1000

FIG. 2. *Peritoneal Exudate*, forty-eight hours after intraperitoneal injection of *Bacterium coli*. Shows increase in mononucleated cells as compared with polymorphonuclear leucocytes, active phagocytosis, and stages in the degeneration of the ingested leucocytes. Film stained by Benda's saffranin and light-green method. × 1000

PLATE V, p 34





exerts, according to this writer, a positive effect (*see* below). To this influence the name **chemotaxis** (or **chemiotaxis**) has been given (p. 621).

If the mesentery of a frog is exposed and irritated, even with normal saline solution, the leucocytic changes described are seen. The saline solution, or even the mere exposure to air, exerts a positive chemotactic action. If, however, the exposed mesentery is washed with a dilute solution of quinine, as first pointed out by Binz (1874), the leucocytes remain globular and do not become adherent to the walls of the vessels. Binz thought that the quinine paralysed the leucocytes, but Disselhorst (1888) showed that, if the leucocytes were removed from the vessels, their amœboid movement was still evident. Apparently, the explanation of this observation is that the quinine had neutralised the previous positive attraction, and a negative chemotaxis had been set up. Besides the attractive force of chemical agents and bacterial products, there are other possible forms of stimuli which may produce leucocytic emigration. In fact, these blood-leucocytes probably respond to stimuli in the same manner as amœbæ and other unicellular organisms, and, therefore, the reactions to light, heat, electricity, and various tactile stimuli must also be regarded as factors which influence the leucocytes in their movements. It has been claimed that surface-tension plays a part in phagocytosis and in chemotaxis. We ourselves have noted that, even during the course of a surgical operation, for example the removal of a tumour from the brain by the use of diathermy or the electro-cautery, polymorphs may escape from the damaged vessels in such numbers as to simulate small " abscesses " or even extensive " purulent infiltration "—a chemotactic action, possibly, of the " electrically-cooked " tissues. This phenomenon may occur within fifteen or twenty minutes in areas of normal brain-tissue removed to allow of access to subjacent or perhaps distant tissues (p. 1058 and Fig. 646).

We have stated above that the **capillaries** in inflamed areas exhibit an **increased degree of permeability** because of damage to their endothelial lining, and that the emigration of the leucocytes into the tissues through these damaged walls is determined by some attractive force outside the vessels. We consider that this force is exerted by some substance which is the product of bacterial activity or of tissue-metabolism ; or, as noted in the preceding paragraph, due to, or perhaps aided by, various chemical and physical factors. The liberation of **histamine** or an " H-substance " identical with histamine from an injured area has long been regarded as a cause of dilatation and increased permeability of minute vessels (Lewis and Grant, 1924).[1] In 1936, Menkin,[2] of Harvard University Medical School, started an investigation to determine whether inflammatory exudates contained any substances which could induce this local vasodilatation and increased vascular permeability. He isolated, " in a form which seems to be relatively free of any gross impurities " (p. 36), a nitrogenous substance which, on cutaneous injection, produced, not only increased capillary permeability, but also active and rapid leucocytic migration.

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[1] Sir T. Lewis and R. T. Grant. " Vascular Reactions of the Skin to Injury," *Heart*, 1924, **11**, 209.

[2] V. Menkin. " Dynamics of Inflammation," Macmillan, New York, 1940. This book deals with many interesting points on the subject of inflammation and contains a very complete bibliography.

This substance, because of its positive chemotactic characteristics, he named "**leukotaxine.**" Its origin is not definitely determined, but Menkin[1] considers that "the present evidence suggests that it is an intermediary breakdown product of protein-metabolism, possibly belonging to the group of relatively simple polypeptides. The active factor manifests no property in common with histamine or presumably with the hypothetical H-substance assumed to be closely related to histamine. Observations do not substantiate Lewis' hypothesis of histamine or of its closely related H-substance as the primary cause of increased capillary permeability in inflammation." [1] Further, Menkin holds that this leukotaxine has no influence on the phenomenon of phagocytosis and apparently no relation to the number of leucocytes found in the blood in inflammatory conditions. Such blood-leucocytosis is caused by some factor which stimulates the production of leucocytes and is thermolabile in character, acting primarily on the bone-marrow, and present in the inflammatory exudates and itself originating from tissue-injury at the site of the inflammatory reaction. The active principle of this factor, according to the researches of Menkin, is either a pseudoglobulin or, at least, is associated with that protein-fraction. The presence of opsonins or tropins in normal and immune sera enhances the phagocytic properties of both polymorphonuclear and mononuclear leucocytes (*see* pp. 128 and 133). It is suggested that these phagocytosis-promoting substances, by being deposited on the surface of bacteria or particles of various kinds, so alter the surface-tension between the cell and the particle to be ingested that phagocytosis is facilitated. In regard to the subsequent replacement of the polymorphonuclear leucocytes by mononuclears, the view of Menkin (*loc. cit.*, p. 88) is that : "The underlying mechanism involved in this basic phenomenon depends on the production of a local acidosis in the inflamed area."

III. INFLAMMATION IN NON-VASCULAR AREAS

This is best studied in the cornea, which in health is a transparent non-vascular membrane, composed of parallel laminæ of fibrous tissue. Between these laminæ are numerous lymph-spaces and channels, and also somewhat flattened connective-tissue cells—the corneal corpuscles. The lymph-channels communicate freely with one another and with lymphatics at the periphery of the cornea. It is difficult to produce damage to the cornea without so injuring the conjunctiva that the conjunctival inflammation, which necessarily follows, obscures the corneal changes. Where damage is produced without setting up inflammatory changes, no sign of leucocyte-emigration appears within twenty-four hours, and no sign of peripheral congestion. The corneal corpuscles at the centre of the injured area, however, show degenerative and destructive changes, whilst those nearer the periphery become enlarged. Later, proliferation takes place in the peripheral healthy corneal corpuscles. These send prolongations into the necrosed area, and thus complete repair is brought about—the only cells taking part in the process being the fixed connective-tissue cells. If the damage is more extensive, and especially if bacteria are present, an area of opacity around the focus of injury is produced. Polymorphonuclear leucocytes are found in abundance in this area, and also migrating along the surface from the conjunctival vessels, though there may be, as yet, no congestion of the peripheral vessels. With still more severe irritation, in addition to the production of the central opacity, the vessels at the periphery of the cornea become dilated and engorged with blood, and leucocytes are seen migrating from them along the lymph-spaces between the various layers of the cornea to the site of irritation. There is also transudation of lymph, with which the lymph-spaces are distended, and, by absorption of which, the connective-tissue fibres become swollen and œdematous. The corneal corpuscles undergo proliferative changes early in the process, and, during the second day after the injury, they can be seen as wandering-cells in the damaged area. These cells act as phagocytes. According to Adami (1907), the "lymphocytes are not visible till the fourth day, and they do not so much pass out of the vessels as from the sheath of lymphoid tissue surrounding them," *i.e.*, from lymphocyte-like cells present, it may be in small numbers, in the perivascular spaces. New capillaries, arising from the vessels at the periphery, penetrate the corneal structures, and are accompanied by proliferated corneal corpuscles. Thus repair is brought about. The experimental evidence proves that the changes in a non-vascular area are analogous to those seen in any vascular part. The dilatation of the vessels at the margin, the lymph-transudation, and the leucocyte-emigration take place in both ; and the character of the migratory leucocytes and their reaction-times also correspond.

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[1] *Loc. cit.*, p. 48.

SEQUELÆ OF THE ACUTE STAGE OF INFLAMMATION

Phenomena following the Inflammatory Process. If the irritant be removed, the process may at any period become arrested and all the phenomena subside, unless the tissues have suffered great damage. The condition may, however, spread widely by way of the lymphatics or blood-vessels, and, from a slight infection, widespread diffuse inflammation and general septicæmia sometimes occur; or the infection becomes localised, and abscesses or ulcers are formed. Several factors determine the localising or the spread and dissemination of the processes. Among these are the nature of the irritant, the vitality and the nature of the tissues involved, the situation of the inflammatory focus, and the resisting power of the individual.

SUPPURATIVE INFLAMMATION AND ABSCESS-FORMATION. Suppuration is caused by the pyogenic or pus-forming organisms, and, in the majority of such lesions, the causal bacteria are demonstrable in the pus or discharge. In not a few cases, however, the pus is sterile—the bacteria having been killed and disintegrated by the substances produced by themselves or by the tissues of their host. Sometimes the bacteria are found in the surrounding tissues, though absent from the necrotic or purulent focus, and it has been shown that these bacteria may remain latent for long periods, causing apparently very little or even no reaction, though at a later period relapses or recrudescences may supervene. This has been noted particularly in many cases of wounds during war, especially where foreign bodies, such as bullets or bits of cloth, have remained in the tissues. In agranulocytosis (p. 636), because of the imperfect maturation of polymorphs, suppuration and abscess-formation are impeded or prevented.

The formation of pus may take place *without* the intervention of bacteria. It has been shown that certain chemical substances—toxins, sterilised cultures, etc.—have a positive chemotactic power for polymorphonuclear leucocytes, and may produce definite abscesses, which, however, are always localised and heal rapidly. Among the substances which produce them are silver nitrate, zinc chloride, compounds of mercury, oil of cloves, mustard, turpentine and petroleum.

Suppurative inflammation, however, is best studied by experimental injection into the subcutaneous tissues of small quantities of living pyogenic bacteria. The usual inflammatory changes—dilatation of vessels, exudation of lymph, and emigration of leucocytes—are seen within a few hours. In about twenty-four hours after the injection, there may be considerable multiplication of the bacteria, and the polymorphonuclear leucocytes are seen in great numbers in all parts of the infected area, separating the fibrillæ of connective tissue. The vessels are much congested, and the connective tissue becomes swollen and œdematous. Near the marginal zone, there are usually numerous mononucleated cells. In about forty-eight hours, a well-defined, though, it may be, small, **abscess** has developed. The centre of this shows densely-packed leucocytes (Plate VI, facing this page and Fig. 14), mainly of polymorphonuclear type, some of which show definite karyolysis and karyorrhexis ; and mingled with these are the bacteria, many of them free, but others englobed in the cytoplasm of the leucocytes. Fragments of broken-down and degenerating tissue (*e.g.*, muscular, fibrous, etc.) may be present in this central degenerated cellular area. At the periphery, external to this **pus** or central mass of cells, necrotic tissue and debris, the capillaries are congested ; and, surrounding these vessels, are numerous leucocytes, of both polymorphonuclear and mononuclear types (Plate VI). At a period of from four to six or ten days, the degenerative changes in the leucocytes and the necrotic changes in the original tissues become much more marked, and a definite wall of **granulation-tissue** is in process of formation (Figs. 15 and 644–5, pp. 39 and 1055–6). This wall contains many new capillaries, and newly-formed connective tissue with numerous fibroblasts and other mononucleated cells (Plate VI, facing this page,

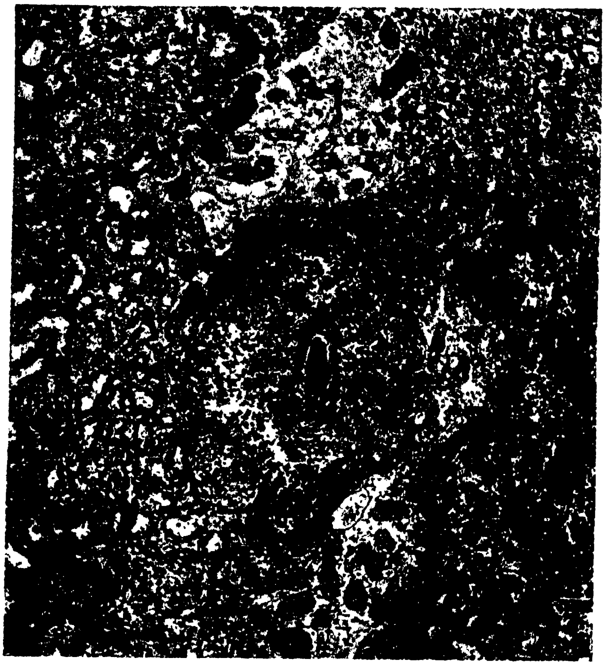


FIG. 14. Acute embolic abscess in the kidney, showing central plug of bacteria, with surrounding mass of leucocytes. × 80.

DESCRIPTION OF PLATE VI

PLATE VI

(From thesis by the late J. W. Dawson, M.D.)

Section of the *wall of an abscess* (small and large scale drawings).

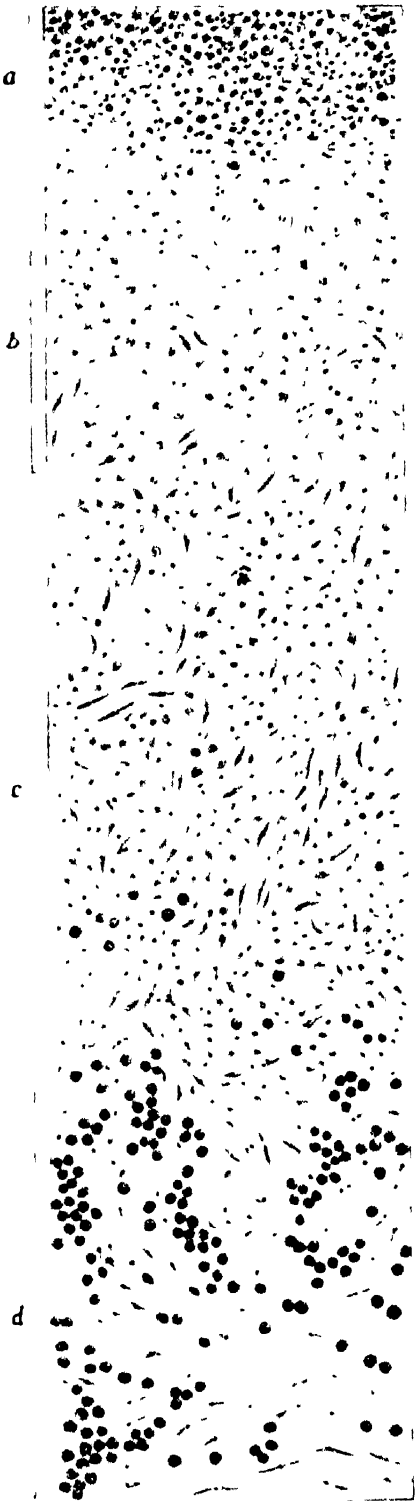
a. Purulent material (polymorphonuclear leucocytes and other degenerated cells).

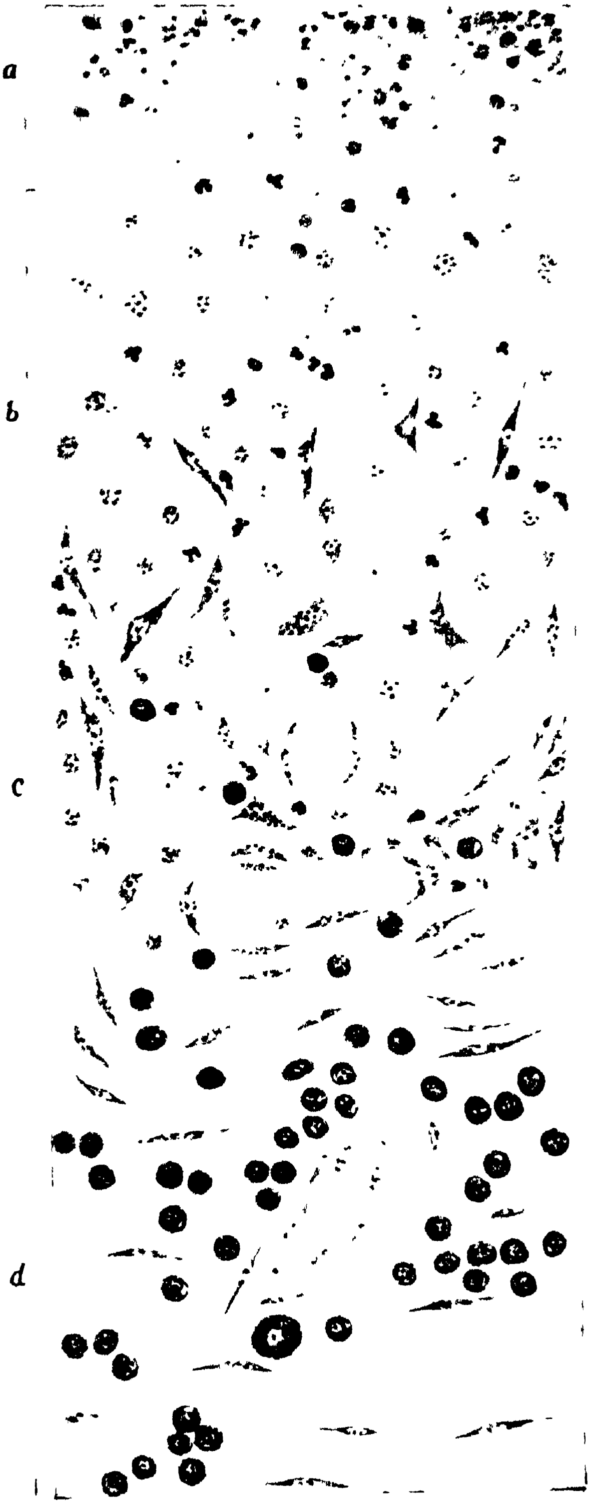
b. Vacuolated phagocytic cells with some polymorphonuclear leucocytes and a few fibroblasts.

c. Some vacuolated phagocytic cells, fibroblasts, young capillaries and a few mononucleated cells.

d. Fibroblasts, now arranged parallel with surface, young blood-vessels and numerous mononucleated (plasma-) cells. (Stained with methyl-green, pyronin and resorcin.)

PLATE VI. p. 38.





and Fig. 15 below). If the area of irritation be near the surface either of the skin or of a mucous membrane, the superficial layers may become necrosed, the dead tissue being cast off as a **slough,** and an **ulcer** may thus be produced. The nature of the minute changes in the abscess and in the ulcer are really identical, and the floor and edges of the ulcer and the wall of the abscess show a similar formation of granulation-tissue.

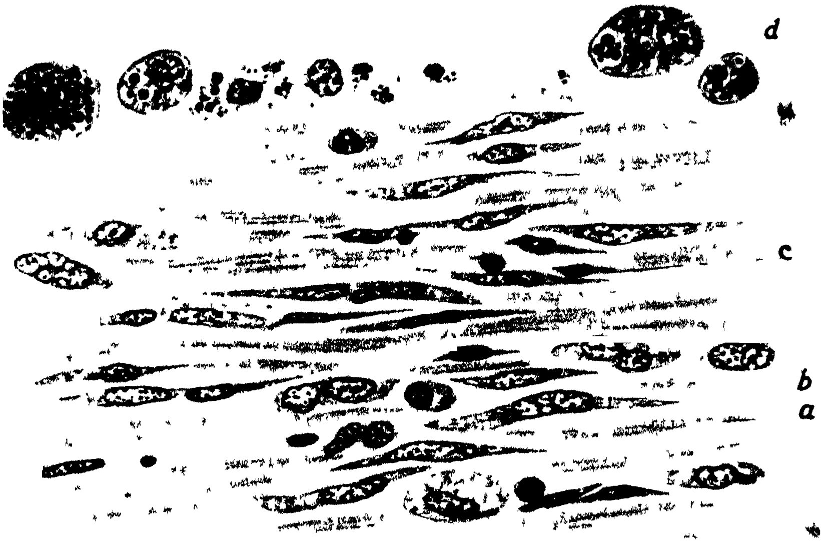


Fig.1.

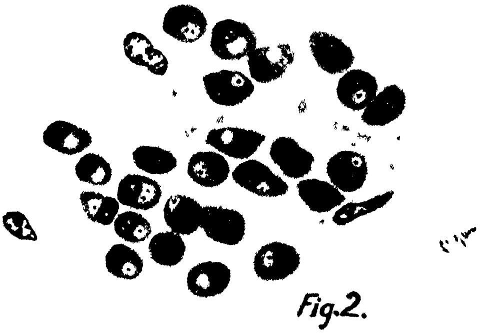


Fig.2.

Fig. 15. *Wall of an old abscess-cavity.* (From thesis by the late J. W. Dawson, M.D.)
Fig. 1. *a.* Fibrous laminæ.
b. Connective-tissue cells.
c. Mononucleated cells, becoming elongated and spindle-shaped.
d. Phagocytes containing pus-cells at border of the purulent exudate.
Fig. 2. Group of plasma-cells in wall of abscess. × 700.

A **Pustule** is a localised cutaneous lesion which is produced by suppuration, usually in a pre-existing papule or vesicle. Such small abscesses may originate in the epidermis, in the dermis, or in a hair-follicle or sebaceous or sweat-gland; and may be single, in groups or scattered over wide areas.

Individual pustules vary greatly in size, and neighbouring pustules may coalesce. Pyogenic cocci are the commonest causal organisms, especially staphylococci. For detailed descriptions of special forms of pustule, *e.g.*, those of pustular acne, sycosis and impetigo, books on Dermatology may be consulted. For a description of **malignant pustule,** *see under* Anthrax, pp. 505–7 and Fig. 293, p. 506, and of the **pustular eruption of smallpox,** *see* pp. 100–1.

A **Boil** or **Furuncle** is a similar but usually a severer form of localised inflammation, commencing as a rule in a hair-follicle or skin-gland, in which the organisms — most frequently *Staphylococcus aureus* —produce necrosis of the affected follicle or gland and usually also of a varying amount of the surrounding tissues, forming the characteristic **central slough** or **core,** which becomes separated from the neighbouring structures by the suppurative process. A "ripe" or "mature" boil thus consists of a central necrotic core, surrounded by a zone of suppurative softening, outside which is formed a wall of granulation-tissue which merges with the neighbouring healthy tissues. After the separation and discharge of the central slough by rupture of the boil or by surgical incision, the suppurating cavity usually contracts rapidly and becomes filled in with granulation-tissue, and healing takes place by the transformation of this into connective-tissue.

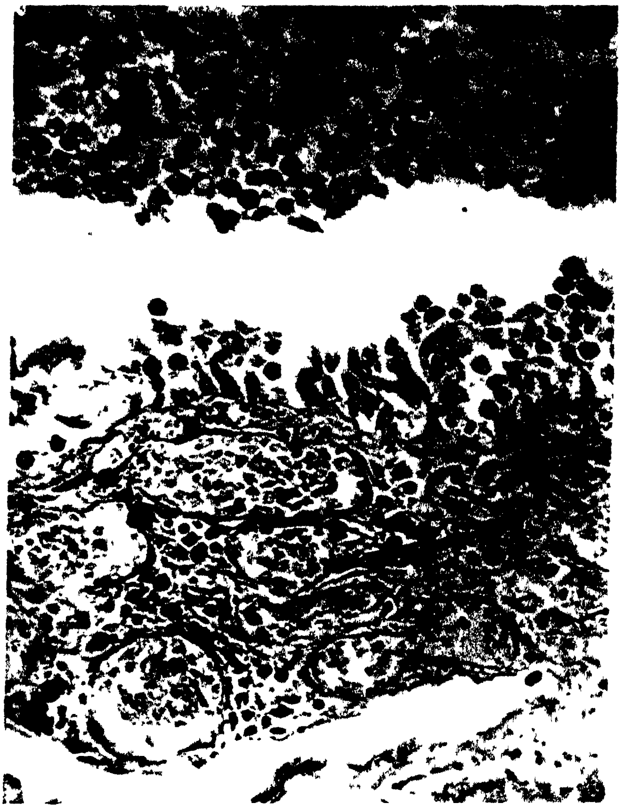


FIG. 16. Catarrhal Inflammation: Acute Bronchitis, showing congestion of vessels and desquamation and degeneration of the epithelial cells. (The large blank area is an artefact due to shrinkage and retraction of exudate in lumen from the wall during embedding process.) × 300.

A **Carbuncle** presents similar characters, but the infection extends more deeply into the subcutaneous tissues, often with the production of multiple and extensive necrotic cores. The surrounding inflammatory reaction is more intense, and toxic absorption is liable to supervene. Such boils and carbuncles tend to occur especially in debilitated persons, particularly in diabetics.

Pus is usually alkaline in reaction, and contains, not only the proteins normal to the blood, but also derivatives from these proteins, *viz.*, peptones and other albumin-containing substances. Fatty acids and cholesterol, as well as pigment derived from red blood-corpuscles, may be present. The cells are abundant, and are mainly of polymorphonuclear type, in different stages of degeneration and necrosis, but there are in addition various types of mononuclear cells. Portions of muscular, fibrous, or elastic tissue, undergoing necrosis, and fibrin, may also be found. The fibrin undergoes digestion by various ferments formed in the pus and, therefore, is usually in small quantities only.

CATARRHAL INFLAMMATION (p. 192).[1] This type of inflammation affects especially the **mucous membranes** of the respiratory, gastro-intestinal and portions of the genito-urinary tracts, and is usually characterised by an increase in the discharge of mucin from the goblet-cells, and degeneration and desquamation of the epithelial cells lining the tracts. The degeneration and desquamation are such prominent features that the term **desquamative catarrh** has been applied to this form of inflammation, and conditions other than those affecting mucous membranes, in which these epithelial changes are present, are spoken of as " catarrh," as for example catarrh of the tubules of the kidney. If the term is applied in its strict sense to an inflammation of a mucous membrane, it must, of course, be recognised that the submucous tissues will also be involved. The basement-membrane becomes swollen from absorption of fluid from the exudate, the subjacent vessels are engorged, and there may be considerable migration of leucocytes through the altered mucosa. In the lumen of the affected tube or canal the secretion will vary in amount and in consistence. It may be thick, tough and mucinous, or, if diluted with serum which has exuded from the dilated vessels, it is more watery. It will contain, as we have noted, degenerated and desquamated epithelial cells, either single or in sheets, together with varying proportions of polymorphonuclear and other types of inflammatory cells. If the inflammation is severe, the secretion may be blood-stained ; and, if the leucocytic infiltration is considerable, it may be muco-purulent or purulent. Later, the surviving epithelial cells of the mucous membrane, usually those of its deeper layers next the basement-membrane, may proliferate, and ultimately complete recovery be effected.

CHRONIC INFLAMMATION. Following the **exudative phase** of acute inflammation, complete **recovery** may ensue, but the common sequel is a certain amount of **proliferation** of the connective-tissue cells of the part. The degree of this reaction depends on the intensity of the irritant and also on the length of time over which it acts. If the irritant is of low intensity and its action of long duration, it does not produce an acute reaction, but the cells are stimulated to proliferate. A similar result will follow if the irritant, which may have produced originally an acute inflammation, persists in the tissues. The latter process is well illustrated in inflammation of bone, an acute osteomyelitis, it may be, becoming a chronic infection and the staphylococci persisting for long periods (p. 1203). In the central nervous system, analogous changes take place in the glial supporting tissue (p. 1059 *et seq.*).

The irritants may be bacteria, toxins, inorganic chemical substances or particulate foreign bodies. (1) A slowly-acting **bacterial irritant,** such as the organisms of tuberculosis or of syphilis or certain types of streptococci, the two former producing granulomata (p. 55), the latter chronic inflammation, for example, of the gall-bladder or the valves of the heart. (2) A **mild toxin** or a **chemical substance** such as lead. The former is probably the more immediate causal factor of cirrhosis of the liver, and the latter of some of the pronounced changes in some varieties of chronic nephritis. (3) **Foreign bodies,** as for example silica-, coal- or asbestos-dust, which, acting over long periods, cause overgrowth of dense fibrous tissue, especially in the lungs (p. 540 *et seq.*).

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[1] From the Greek *κατάρροος*, *katarrhoos* (contracted to *κατάρρους*, *katarrhous*), down-flowing, meaning originally a "running" or morbid discharge, from *καταρρεω*, *katarrheō*, to flow down. When the running was at the nose, it was called a *κόρυζα*, coryza.

All these types of chronic inflammation may have been preceded by degenerative changes such as cloudy swelling and necrosis (the **alterative phase** in inflammation), and therefore the final lesion is sometimes regarded as a **replacement-** rather than as a **productive fibrosis** (**reparative phase**) (see below).

Histologically, the chronic inflammatory lesion is at first **cellular,** spindle-cells or fibroblasts predominating ; but gradually it becomes more and more definitely **fibrous** until eventually there is pronounced thickening of the collagenous fibres, with relatively few cells. The vascularity varies greatly. In some lesions the new vessels are abundant ; whereas in others the tissues are comparatively non-vascular. When the vascularity and cellular character are pronounced, the condition is described as **subacute**. The cells are mainly histiocytes, plasma-cells and collections of lymphocytes (" small round-celled infiltration "). In the later stages, the new fibrous tissue undergoes contraction, and the affected organ or other site of the lesion is hard, shrunken and possibly scarred.

PARENCHYMATOUS INFLAMMATION.[1] This term has been applied to acute, subacute, and chronic changes which affect the special functioning-cells of a part. Many of the changes so described are largely degenerative in character, and are brought about by the direct action of toxins, by impaired vascular supply, or by altered metabolic processes. They are practically always associated with changes in the supporting-tissues and in the vessels.

REPAIR

REPARATIVE CHANGES IN INFLAMMATION. Repair of an injury may be direct, that is, may take place without the essential phenomena of inflammation being present. Thus, an injury of the cornea, as stated on p. 36, may be completely repaired merely by a proliferation of existing corneal corpuscles. Usually, however, the damage will have caused some degree of reaction, and, as a result, there will be deposits of inflammatory products and destruction of tissue ; and, before complete healing can take place, there must be removal or absorption of the exudate or of the damaged tissue. As has been previously stated, the macrophages are the principal agents in this removal, but vascularisation and the development of fibroblasts are important factors in the absorptive and healing process.

The cause of the cell-proliferation which is so characteristic of repair has been attributed to the action of chemical stimulants derived from the damaged tissues, and of the infecting organisms and the migratory cells. Carrel states that these growth-producing substances, which he has named **trephones,** are liberated from the leucocytes, especially the lymphocytes and macrophages. There are differences of opinion as to the types of cell which take part in the formative processes of repair, but experimental evidence seems to establish the position that the polyblasts, the plasma-cells and the macrophages do not take any active part in these and that the principal cells concerned are the fibroblasts or fibrocytes and the endothelial cells lining the blood-vessels and lymphatics. These reparative changes are well illustrated in the healing of wounds.

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[1] *See second footnote on p.* 1010.

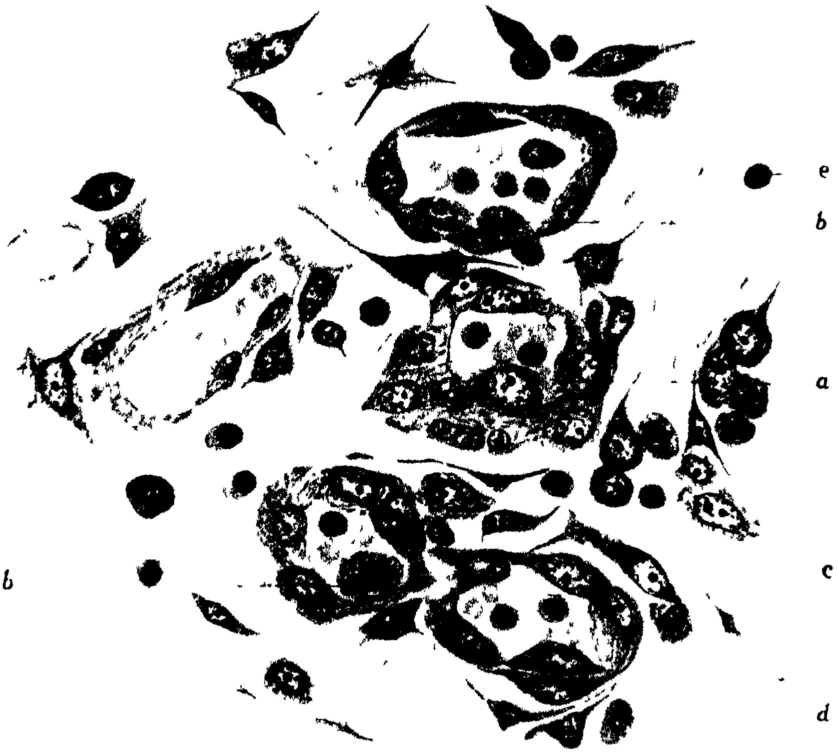


FIG. 17. *A Group of Dilated Vessels at the Margin of a Wound* (twenty-four hours). (From thesis by the late J. W. Dawson, M.D.)

a. Swollen endothelial cells. *b*. Endothelial cell in mitosis. *c*. Fibroblasts. *d*. Mononucleated cells. *e*. Lymphocyte-like cells. × 1,000.

WOUND-HEALING :—

(*a*) **In an Incised Wound.** The processes are best studied in the case of an incised wound which is not thoroughly aseptic, and where the surfaces are not accurately in apposition. During the first twelve hours, the surfaces of the wound become glued together by blood and by coagulated lymph which has exuded from the dilated peripheral vessels. The margins of the wound are red and slightly swollen. This is due to the dilatation of the minute vessels and to the exudation of lymph. Leucocyte-emigration is also seen at this stage—the leucocytes passing into both the lymph and the surrounding tissues for some distance. The vascular endothelium and the fixed connective-tissue cells show swelling, mitosis and other proliferative changes even during the first twenty-four hours, and these changes become more pronounced later (Figs. 17 and 18). At about the same period after the infliction of the wound, vascular buds (Plate VII, p. 48 and Figs. 17 and 18) are given off from the minute vessels at the periphery. At first these buds are conical solid masses of

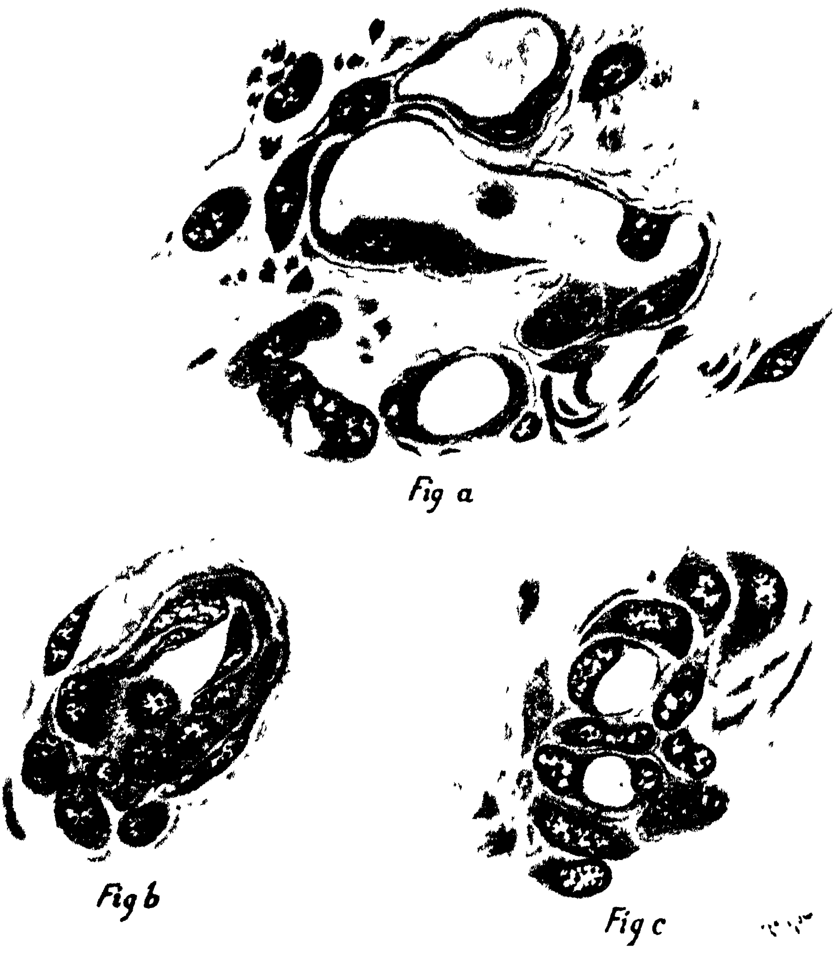


FIG. 18. *Group of Budding Capillaries.* (From thesis by the late J. W. Dawson, M.D.)

Fig. a. Vessel with two endothelial cells in mitosis, one of which represents a vessel-bud.

Figs. *b.* and *c.* Nucleated protoplasmic buds in connection with small vessels.

× 1,000.

protoplasm with nuclei (Fig. 18, *b* and *c*). The nuclei and the cytoplasm undergo segmentation, and thus form columns of endothelial cells. These columns become opened up by separation of the endothelial cells, the channels thus formed being continuous with the lumen of the vessel from which the endothelial bud arose. From the distal end of these buds, long protoplasmic processes grow into the coagulated lymph and blood, and anastomose with other similarly-formed processes, so as to make a network in the fibrin. In these protoplasmic processes the nuclei and cytoplasm segment and, as in the

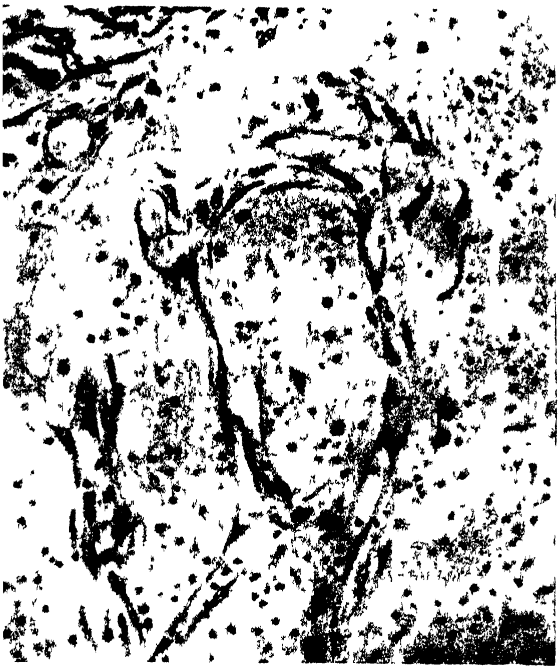


FIG. 19 Healing wound, showing capillary-loop in early granulation-tissue. × 200.

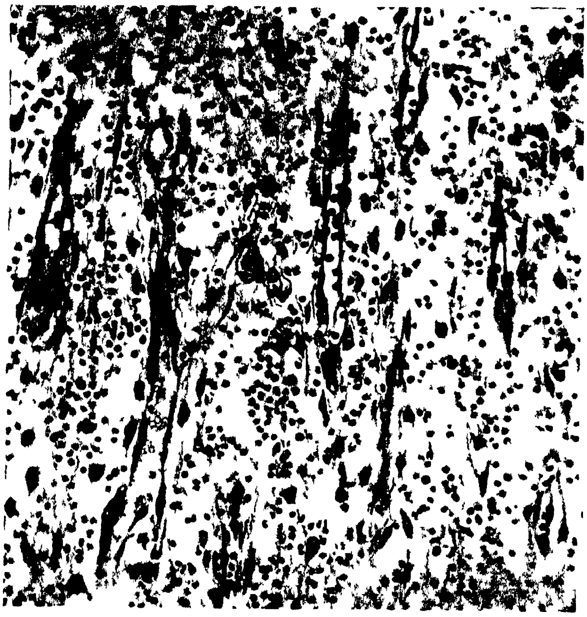


FIG. 20. Healing wound, showing granulation-tissue, with thin-walled vessels, leucocytes and proliferated connective-tissue cells. × 200.

original buds, the endothelium thus formed becomes the lining-membrane of this further extension of the capillary system. This new capillary-network may be well developed in thirty-six hours (Figs. 19 and 20), and even in

SALAR JUNG

twenty-four hours there is abundant formation of vascular buds, and of swelling and mitosis of the endothelium of the developing vessels. Round the new vessels, the exudate of lymph undergoes solution and absorption (Fig. 25). As the capillaries develop, they become surrounded by an adventitia probably derived largely from the proliferation of fixed connective-tissue cells or fibrocytes, which readily re-assume their functions as fibroblasts, producing collagen-fibres and arranging themselves alongside the capillaries (Figs. 20 and 21). Much of the exudate is removed through the agency of this branching capillary-network, and replaced by the newly-formed fibroblastic tissue. Thus, an early **tissue** is formed. In this the vessels are thin-walled, composed merely of endothelium, or of endothelium with a few adventitial cells, and, in consequence, dilatation and rupture are common. These provisional capillary-loops tend to disappear when the lymph and blood have been absorbed. Meanwhile, more vessels have been forming, also by outgrowths from the pre-existing vessels; and these new vessels, together with those surviving from the earlier set, become arranged in a more regular fashion at right-angles to the surface. They are supported by accompanying fibroblasts and by a mass of proliferating fibroblasts formed first in the deeper parts of the wound and arranged in parallel layers at right-angles to the vessels (Plate VII, p. 48 and Fig. 21). In this manner, in from thirty-six to forty-eight hours, the opposing surfaces of the wound are, as it were, "sewn" together. The parallel layers of

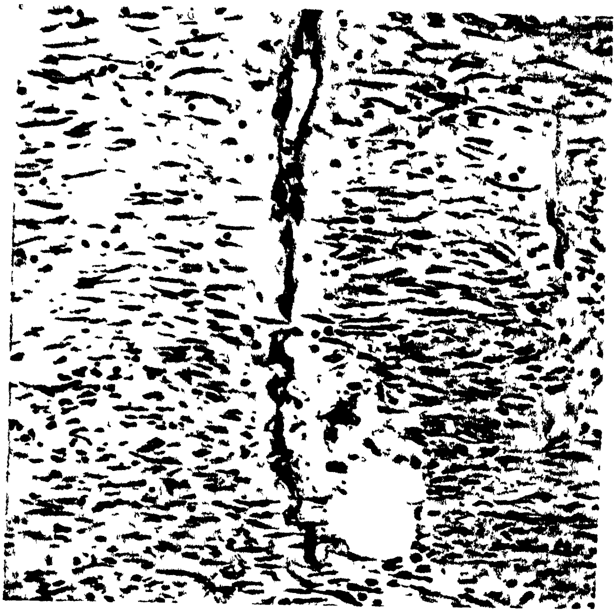


Fig. 21. Healing wound, showing new vessel with slight adventitial coat, and parallel layers of spindle-shaped cells. The clear spaces at lower part are surviving fat-cells. × 200.

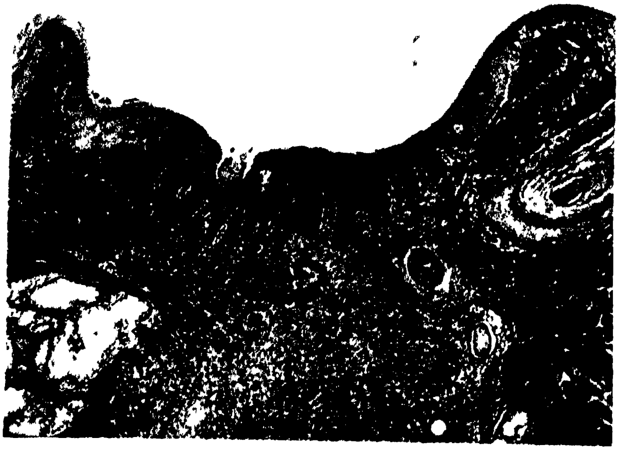


Fig. 22. Healed wound, showing dense fibrous tissue (scar-tissue) with epithelial covering. × 35.

spindle-shaped fibroblasts possess long processes, have a vesicular nucleus and abundant cytoplasm, and are formed from the pre-existing connective-tissue cells. Later, the vessels show thickening of the inner coat and gradual shrinkage and disappearance. In three to five days, definite collagen-fibrils are seen running parallel with the long fibroblasts. Tissue-cultures show that the formation of these fibrils probably takes place between the layers of cells by an alteration in the colloidal-sol which has been secreted by the cell. Gradually the cellular character diminishes, and, in from three to four weeks, cells and vessels have disappeared, and are replaced by dense white fibrous tissue.—**Scar-Tissue** (Fig. 22 and Plate VIII, p. 50, Fig. 2).

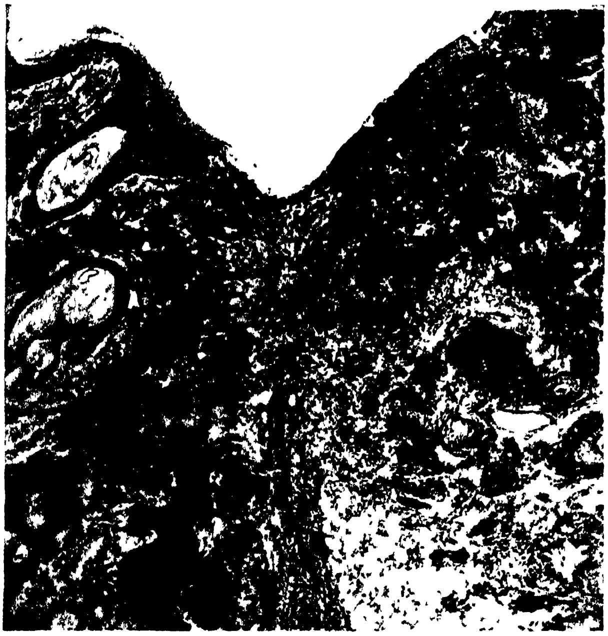


FIG. 23. Incised wound of four days, showing preliminary repair of epithelium, cellular infiltration of tissues, etc. × 35.

Epithelial Cells. Even at an early period, *e.g.*, in twenty-four to forty-eight hours, proliferation of the epithelial cells at the edges of the wound takes place, and these new cells extend over the surface from the periphery inwards. At first, they are entangled in the lymph and blood, and, becoming swollen and œdematous, they tend to perish. As soon, however, as a supporting structure is formed, they grow over the surface as a thin pellicle, and, from this, if the wound is not too extensive, a complete covering of epithelium is developed.

(*b*) **In an Ulcer,** the healing process is essentially the same as that just described for an incised wound. The differences are mainly that, in the healing of the ulcer by granulation, there is a larger gap to be filled up by the new tissue, and, frequently, a considerable amount of damaged tissue to be removed. The process, therefore, is slower, and degenerative and proliferative changes are going on side by side. The connective tissue is formed in larger amount and in a more irregular fashion. Leucocyte-emigration and exudation of lymph are more pronounced, and last for a longer period. The granulation-tissue, however, consists of young newly-formed capillaries surrounded by newly-developed connective-tissue cells ; and it thus corresponds with the new tissue formed in the healing of an incised wound. Further, there occur the formation of definite fibrocytes, the obliteration of the newly-formed vascular loops, and, eventually, the production of scar-tissue.

The granulation-tissue varies in character in different situations according to the nature of the tissue to be repaired, and also according to the nature of the irritant and the length of time during which it acts. In cases where bone or other specially resistant tissues have to be removed, and therefore where preparatory softening must take place, cells of a special type are frequently brought into the field. These are multinucleated masses of protoplasm resembling osteoclasts, and are formed probably by the fusion of several mononucleated phagocytes or by their proliferation and incomplete division and separation. These cells are common in granulation-tissue in any situation, but are abundant more particularly where, as we have said, masses of degenerated structures or foreign bodies of a resistant character have to be removed (Fig. 24). Where the healing is much delayed on account of the prolonged action of the irritant, the newly-formed tissues are apt to become swollen and œdematous from the accumulation of lymph, or they may undergo " mucinoid " or " myxomatous " degeneration. In such cases, too, the more acute phenomena—leucocyte-emigration, cellular degeneration, and the

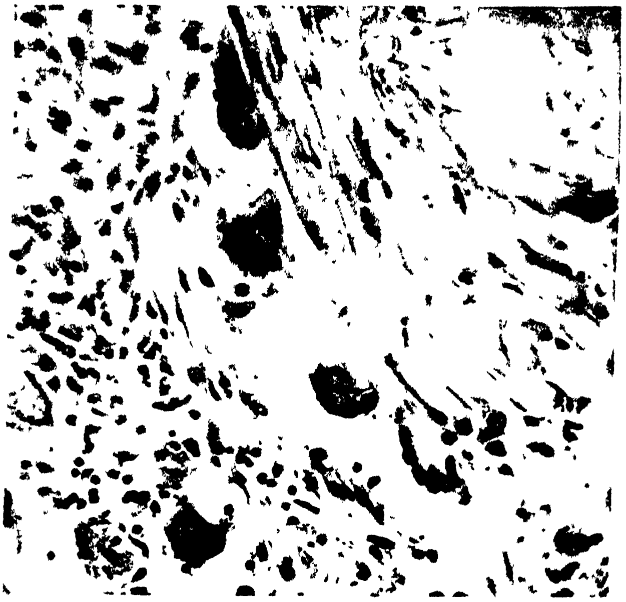


FIG. 24. Giant-cells bringing about the absorption of muscle and a foreign body—a piece of catgut. × 300.

DESCRIPTION OF PLATE VII

PLATE VII

(From thesis by the late J. W. Dawson, M.D.)

FIG. 1. *Structure of Granulation-tissue* (small and large scale drawings of sections).

e. Surface layer of fibrin not organised, and still showing blood-corpuscles and leucocytes.

d. Similar to (*c*), but with vessels in the initial stage of formation and few in number.

c. Intermediate layer with new vessels and fibroblasts mainly parallel with the vessels.

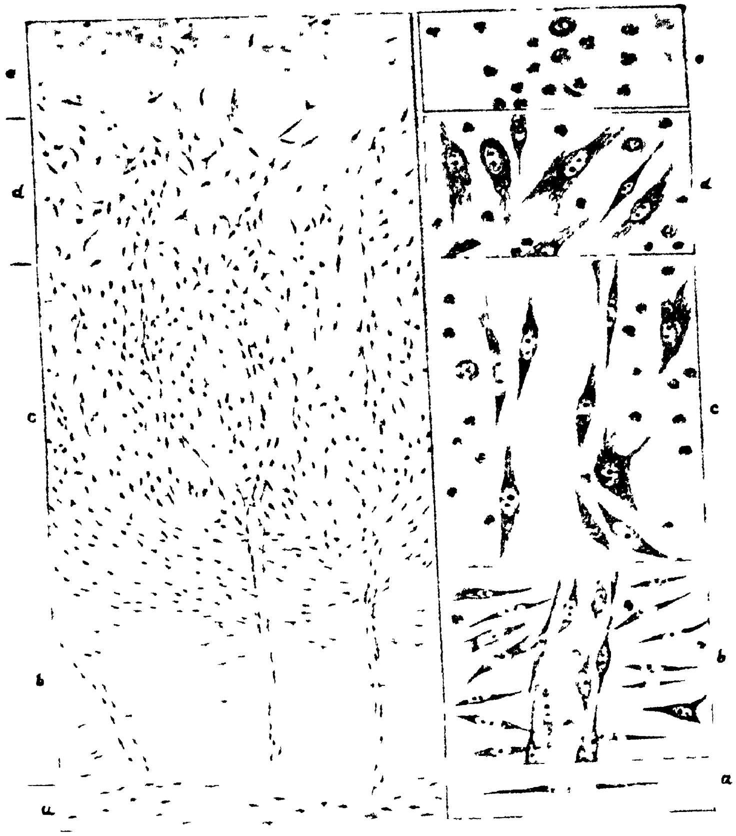
b. Deep layer with fibroblasts at right angles to the vessels. Some surviving fat-cells are shown.

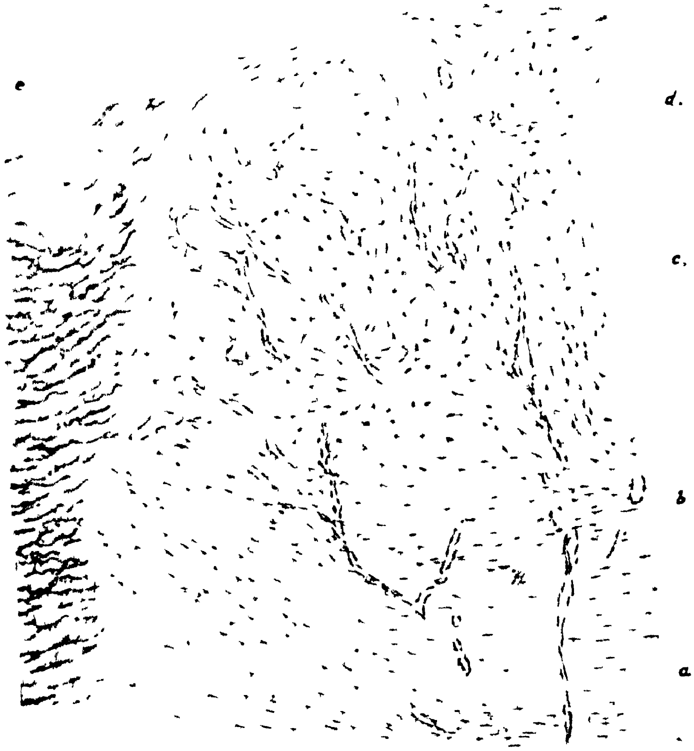
a. Normal tissue.

(Stained with methyl-green, pyronin and resorcin.)

FIG. 2. *New Formation of Blood-vessels in Granulation-tissue.* Note the development of the vessels, etc., in the different layers, *a, b, c, d, e.* (Stained with methyl-green, pyronin and resorcin.)

PLATE VII, p 48.





formation of pus—predominate over the proliferative changes; and hæmorrhage is a common occurrence on account of rupture of the ill-supported capillaries. In wounds infected by the bacillus of tuberculosis or by the organism of syphilis, certain characteristic features, *e.g.*, the presence of **giant-cells** and **caseation,** are usually found in the granulation-tissue; and the growth of the fibrous structures may be modified considerably.

THE ORGANISATION OF AN INFLAMMATORY EXUDATE, *e.g.*, the exudate which forms on the surface of the heart in acute pericarditis or that lining the wall of an abscess.

If, a few days after organisation has commenced, a suitably stained section of the exudate and the adjacent tissues be examined, several distinct layers can be demonstrated:—

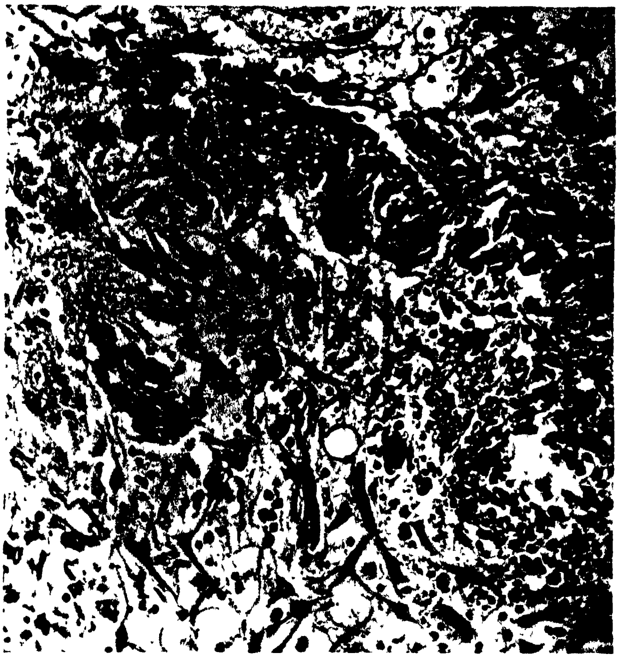


FIG. 25. Organisation of an inflammatory exudate, showing absorption of fibrin, and the presence of rounded and spindle-shaped cells. Note the irregular masses of fibrin at places. × 200.

i. An external, darkly-stained zone, varying in thickness, composed of a network of unaltered, or of granular, fibrin, in which are entangled varying numbers of polymorphonuclear leucocytes (Plate VI, *a*, p. 38).

ii. Immediately under this layer is a second zone, which stains less intensely. In this, the cells are more abundant and the fibrin is distinctly granular. There are a few capillaries, and, round these, where absorption is taking place, the fibrin appears somewhat homogeneous, and stains faintly. The cells are mainly polymorphonuclears, but some mononucleated cells may also be present.

iii. Deeper still, the capillaries are much more abundant (Plate VII, *c*, *d*, p. 48), and the fibrin has to a large extent disappeared, although remains of it may be seen between the capillaries at certain parts, as small homogeneous, areas (Fig. 25). The cells are more abundant immediately around the vessels, and the mononucleated variety predominates. These cells are irregularly scattered, but some are more flattened and are seen lying parallel to the capillaries. Multinucleated cells are also usually present.

iv. At a deeper level (Plate VII, *c*, *b*, p. 48), the fibrin has completely disappeared, and the capillaries, in many parts, show very distinctly an outer supporting coat of flattened cells lying parallel to their endothelial lining. Between the capillaries, there are numbers of cells irregularly arranged, some of which are rounded or ovoid, with granular cytoplasm, others spindle-shaped, and showing branching processes (Fig. 20, p. 45), while others again are large and multinucleated. Fibrils are also present in varying numbers.

v. At the deepest part of the exudate, the new tissue has become denser.

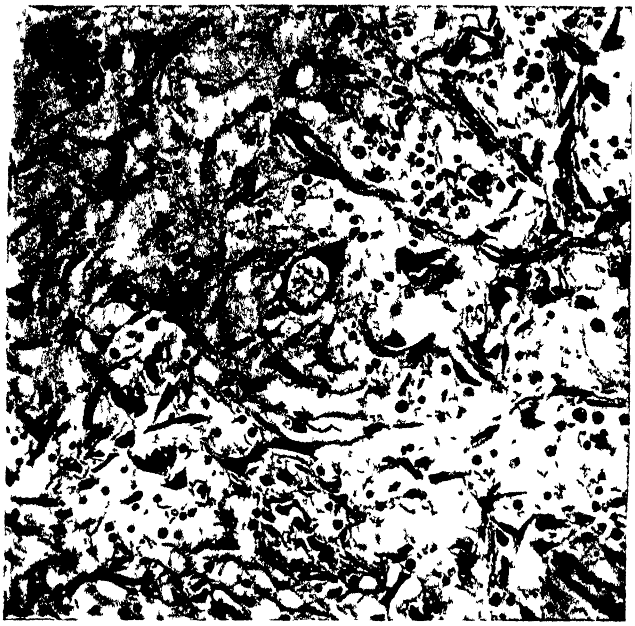


Fig. 26. Granulation-tissue from a healing wound, showing capillaries, and the various kinds of cell described in the text. × 200.

The capillaries are less numerous; the great majority of the cells are flattened, and are arranged in layers parallel with the surface (Fig. 21, p. 46 and Plate VII, *b*, p. 48). These cells are the fibroblasts, and, between them, fibres are seen, which, in the deeper parts, become more abundant, with a corresponding gradual diminution in the size and numbers of the cells The blood-vessels in this layer, as has been indicated, are scanty, and those that are present have a definite adventitia, and, in some of them, proliferation of the endothelium is seen. This proliferation goes on, and, at a later period, the capillaries are to a large extent obliterated. The newly-formed tissue, if on a serous surface such as the epicardium, becomes firmly adherent to that surface, invading it to a certain extent, and no definite line of demarcation between the one and the other can eventually be detected. Here and there, however, some of the endothelium may remain, and, at a later stage, this, in some cases, proliferates

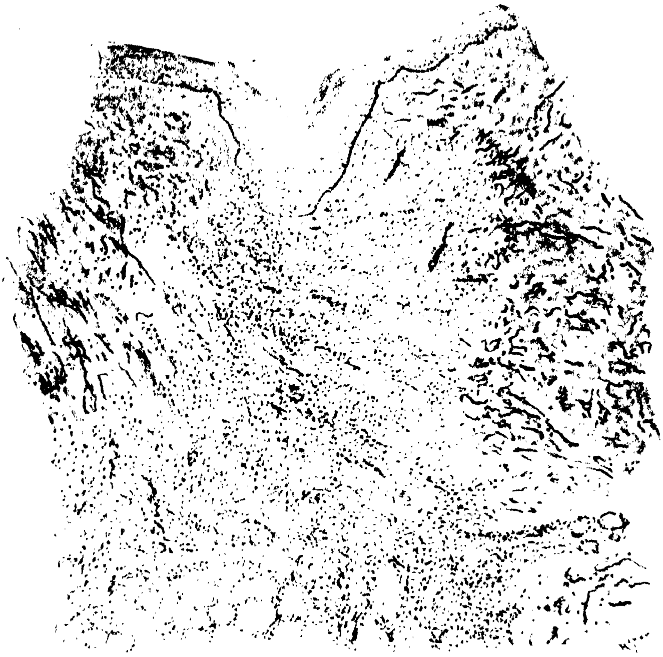
DESCRIPTION OF PLATE VII

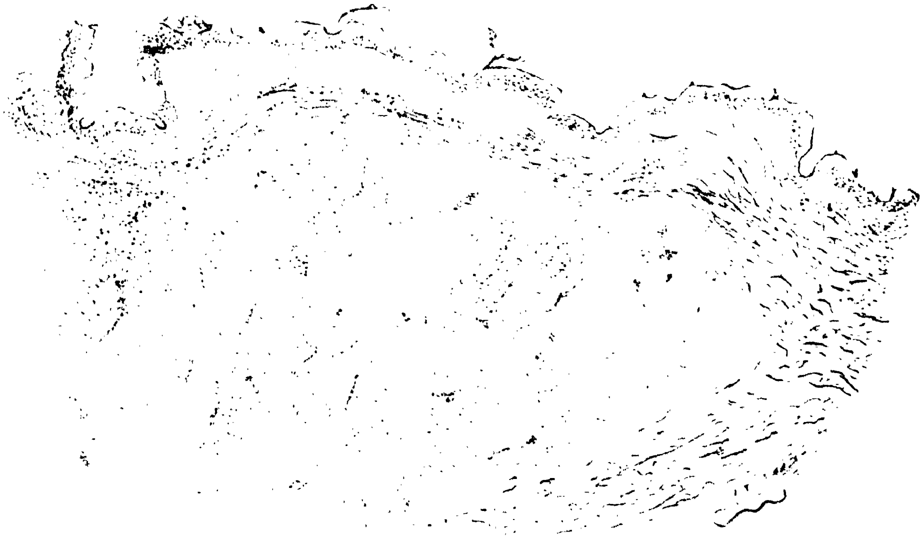
PLATE VIII

(From thesis by the late J. W. Dawson, M.D.)

Fig. 1. *Healing Wound* (seven days). Stained by Weigert's elastic-tissue stain to show the absence of elastic tissue (seen elsewhere as dark blue irregular lines) in the organising area. The pre-existent elastic fibres are shown in the undamaged connective tissue as irregular, wavy dark lines. × 70

Fig. 2. *Healed Wound* (five months). Shows the new elastic fibres meeting across the superficial layers of the scar-tissue, but absent in the deeper parts (Weigert's elastic-tissue stain). × 70





and grows over the surface. Thus, the normal endothelial covering may to a large extent be regenerated. The various layers which have been described are seen best in the organisation of an exudate on the surface of the heart. In other situations, the process may be more irregular in its arrangement, but, wherever organisation is taking place, the formation of capillaries is the early stage, and the capillaries are always formed by budding from pre-existing vessels. The cells, too, are similar in type to those found in any form of granulation-tissue in its later stages.

HEALING IN VESSELS. In the organisation of a thrombus in a vein or artery, the changes are essentially the same as those described in the healing of wounds, but the endothelial lining of the vessel may show special proliferative changes. It may grow over the thrombus, forming a complete covering. If the thrombus only partially fills the vessel, its covering endothelium and the portion of the endothelial lining of the vessel opposite the thrombus may be separated by a distinct space from one another, or may be in contact. If the former, there may be a definite endothelial-lined channel through the thrombosed area ; if the latter, the thrombus may contract and shrink from the wall, and the opening thus produced becomes lined by endothelium forming a new channel through which the blood may flow. Restoration of the channel by this means is, however, not common. The usual course is for organisation of the thrombus to take place, and its absorption to be brought about by cells and young vessels, as in the healing of an ordinary wound. New channels may be formed through the thrombus, and these become lined by

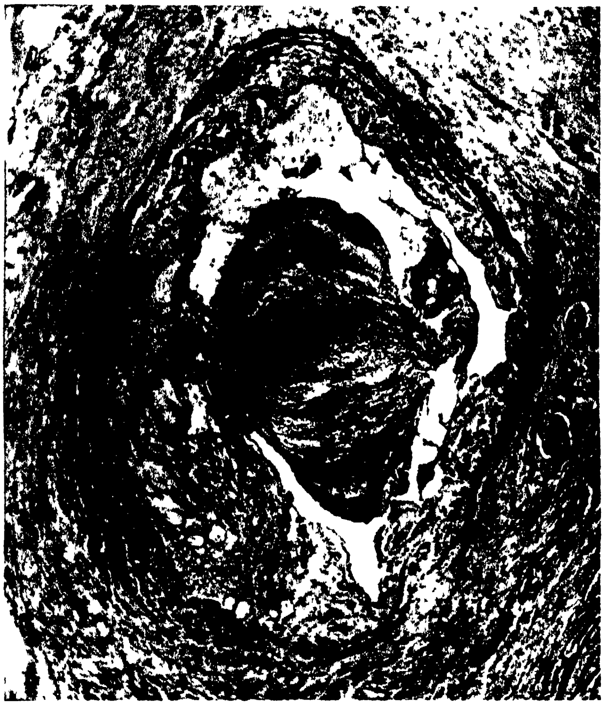


FIG. 27. Thrombus in a vein, showing partial re-opening up of the lumen and organisation. Note the dilated vessels in the organising area (left side). × 40.

endothelium (canalisation). In thrombosis resulting from ligature of a vessel, there is, after a few days, a local proliferation of endothelial and subendothelial connective-tissue cells of the intima, and these cells penetrate into the thrombus in the form of small buds. At a later period, young vessels are seen, and can be traced to the vasa vasorum, from which they arise. The vessels from opposite sides and at different levels come to anastomose, and the thrombus, if not too large, may be absorbed, or the granulation-tissue which is formed may become fibrous and undergo contraction. The fibroblasts formed during this process are usually smaller and more branched than those seen under ordinary conditions in wound-healing (Fig. 28). When the clot is large or is formed in a large vessel, the process of vascularisation is generally incomplete, and the more central part of the thrombus tends to degenerate, become fatty, or even calcareous, and contains granules of blood-pigment.

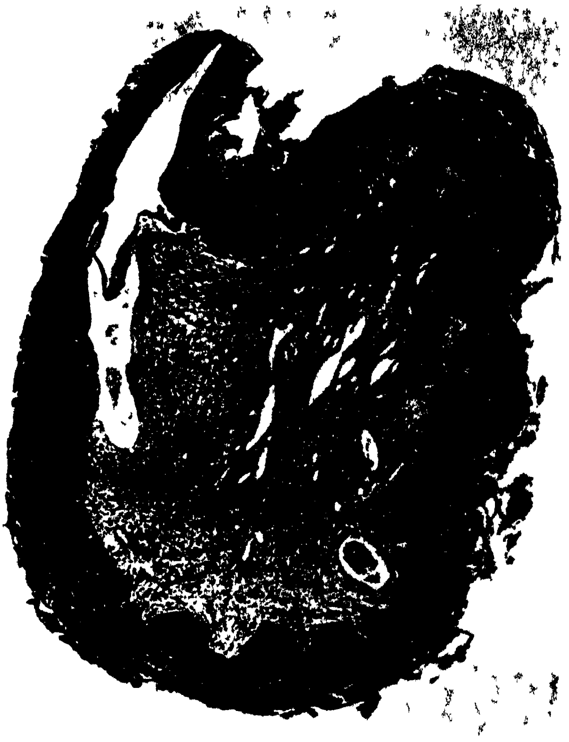


FIG. 28. An organised thrombus in an artery, showing that the organised tissue (granulation tissue) is wholly internal to the elastic lamina. × 40.

HEALING IN SPECIAL TISSUES

As already indicated, the essential processes are identical in all forms of repair, but, in individual instances, there may be certain differences and modifications, dependent upon the nature of the tissue, the character of the injury and also on the extent of the damaged area. Reference has previously been made to repair of the cornea by direct proliferation of corneal corpuscles, without the intervention of inflammatory reactions (pp. 36 and 42).

Elastic Tissue. This can to a certain extent be re-formed by offshoots from the pre-existing elastic fibres—possibly through the agency of cells not yet satisfactorily demonstrated. Milne[1] has pointed out that, in the repair of wounds of the liver, especially of aseptic wounds, a very considerable new formation of elastic tissue takes place, and this, he says, appears to be derived from some pre-existing elastic fibres. Dawson was of opinion that the pre-existing fibres were the main source of the new elastic tissue, and that there was distinct evidence in scar-tissue that elastic fibres are formed from the cells of the part. In chronic changes in the walls of blood-vessels, such as those produced by syphilis, there is often considerable increase in elastic tissue. This re-formation is a slow process, and the new tissue is somewhat ill-formed, and may not function so perfectly as the original elastic tissue (Plate VIII, p. 50). (*See also under* " Fibrotic Thickening of Ligamenta Flava," p. 1223, and Fig. 791 on p. 1224.)

Fatty Tissue. In healing wounds, the fat-cells remain unaltered for a considerable time, but, as absorption goes on, the fatty tissue undergoes mucinoid degeneration and becomes converted into mucinoid or " myxomatous " tissue. It is claimed that new fatty tissue may be formed by the multiplication of old fat-cells. The resulting lipoblasts accumulate a lipin-content as they become older, although when young no fat may be visible in them. The possibilities of functional interplay and morphological adaptation within the supporting-tissue group are so great that it must be concluded that new fatty tissue may arise from indifferent fibroblasts which were not themselves derived from previously existing fatty tissue.

Muscular Tissue:—

Unstriped Muscle. In certain animals, regeneration of unstriped muscle takes place by subdivision of pre-existing muscle-cells ; and, in man, in the middle coat of arteries, in repair, a new formation of muscle must occur ; but in wounds, as a general rule, union of severed unstriped muscle is brought about by the formation of fibrous tissue, and evidence of true muscle-regeneration has not been established.

Heart-Muscle. Wounds in the heart are healed almost exclusively by the formation of fibrous tissue, though multiplication of muscle-fibres by division of the nuclei and subdivision of the fibres in a longitudinal direction may take place to a certain extent.

Voluntary Muscle. In wounds of this tissue, union by fibrous tissue predominates, though some regeneration of the muscle itself may occur. New muscle-fibres are formed at the ends of surviving segments of the original fibres. The nuclei of the muscle-cells leave their position beneath the sarcolemma and become scattered through the interior of a bulbous mass of undifferentiated sarcoplasm at the end of the fibre. This protoplasmic mass may elongate as a whole, or several processes may project from it, but always in the general direction of the long axis of the original fibre. Later, the nuclei assume the peripheral position in the fibre and transverse striations develop. During absorption of muscle-fibres, there is considerable proliferation of the sarcolemma-nuclei (Plate XIX, p. 1246). (*See* Diseases of Muscle, p. 1242 *et seq.*)

Epithelial Tissues. New epithelium is always formed by proliferation and growth of pre-existing epithelium. Squamous epithelium shows pronounced capacity for repair in this way, and, if a few islets of squamous epithelium over the surface of an ulcer escape destruction, regeneration of the whole surface layer may be greatly facilitated. This property of rapid regeneration of epithelium is utilised in the surgical operation of "**grafting,**" and extensive denuded surfaces may become covered by the proliferation and coalescence of a series of localised "grafts." In some of the more highly-specialised epithelial tissues, *e.g.*, ciliated and glandular epithelium, there is considerable power of regeneration. Thus, after recovery from acute bronchitis, there may be complete restoration of the ciliated epithelium ; and, in wounds of the liver, repair by proliferation of existing liver-cells takes place. Also, following both wounds and toxic injuries of the liver, solid cords of cells are produced which at first have the staining-qualities of bile-duct epithelium. Later, some of these appear to be transformed into cords of liver-cells. As a general rule, however, the filling up of gaps resulting from destruction of specialised cells such as those of the liver and kidney, is effected to a large extent by the formation of granulation-tissue and the production of fibrous scars. In some cases, the power of repair is extremely limited, and, where it does occur, the epithelium formed may be of a lower type than that which was destroyed, and thus highly-functioning columnar epithelium may be replaced by a low-cubical, lining variety. In extensive surface wounds, in which the hair-follicles and sebaceous glands have been destroyed, the scar-tissues show an entire absence of these structures. Hyperplastic changes in scar-tissue, known as "cheloid," are described on pp. 185 and 268–9 and 301.

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[1] *See* footnote on p. 763.

Bone. Here a considerable part of the granulation-tissue undergoes special changes. The cells of the granulation-tissue are transformed into osteoblasts, and the intercellular substance becomes impregnated with lime-salts. This imperfectly ossified granulation-tissue or callus[1] is subsequently partially or entirely absorbed, and replaced by more regularly-formed bone with definite Haversian systems—the method of formation being that seen in normal ossification. Ordinary granulation-tissue in which the fibroblasts have been derived from fascial and interstitial connective tissue, has little, if any, power of osteogenesis. When such tissue is derived from periosteum, perichondrium, or the so-called endosteal connective tissue, there may be a marked facility for new bone-formation. (*See* Diseases of Bone, p. 1199 *et seq.*, and p. 1206–7.)

Cartilage. Union is most commonly by fibrous tissue, but development of hyaline cartilage from newly-formed fibrous tissue may occur. This transformation of periosteal tissue to cartilage is seen not infrequently in certain pathological conditions (pp. 303–4 and 1214–18). For the scar-like thickening following upon injury of the **ligamenta flava,** with or without associated **herniation** or **prolapse of an associated intervertebral disk,** either or both of which lesions may cause compression of the spinal cord or nerve-roots, *see* p. 1223 *et seq.* and Figs. 786 to 791, pp. 1220 to 1224.

Nervous Tissues. Repair of these is dealt with in the section on Peripheral Nerves, in the chapter on the Nervous System, pp. 1178–9.

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[1] Latin, *callus*, hardness (of the tissues, in this instance the ossifying supporting tissue) : *cf. callosus*, hard, brawny, callous (originally used especially of the skin).

CHAPTER III

GRANULOMATA

These are a group of pathological conditions in which the lesions are the result of subacute or chronic inflammatory changes, associated with various protective and reparative processes. They may produce considerable masses of new tissue which in some respects resemble or simulate tumours (*see* pp. 1262–4). All of these lesions, however, are infective in nature, and in the majority of them the specific organism has been determined. Further, they are almost always associated with various toxic conditions, *e.g.*, fever, wasting, amyloid and fatty degenerations, etc. These so-called **granulomata** or granulation-tissue " tumours " may be divided into two groups : (*a*) those which develop slowly, the pathological lesions being necrotic or caseous, and the proliferative or reparative changes often pronounced : (*b*) those in which acute inflammatory reaction is present, and the destructive changes—often suppurative in character—are more in evidence than the proliferative.

In the first group are placed Tuberculosis, Leprosy, Syphilis and Yaws, and in the second Glanders, Actinomycosis and other Streptothrix-Infections, Aspergillosis, Sporotrichosis and Blastomycosis.

The nodules or granulomatous masses in the second group are in character intermediate between the purely inflammatory lesions seen in the skin and mucous membranes in a disease such as anthrax, and the caseous nodules of tuberculosis, or the gummata of syphilis. Unlike many other infective conditions, the chronic granulomatous diseases are not self-limited. No spontaneous termination to their course can be predicted. It is because of this capacity of remaining active for an indefinite period that in them there takes place the production of the characteristic " tumour-like " masses of granulation-tissue. Not infrequently, the granulation-tissue thus developed by the body in response to the infective process possesses a character sufficiently distinctive to make it possible to conjecture the nature, and perhaps also the identity, of the causal agent of the particular lesion under investigation, even when that agent has not itself been actually demonstrated in the lesion. As we propose to deal only with the pathological aspects of these diseases, we refer our readers to textbooks on Bacteriology for descriptions of the morphology and of the cultural and staining characters of the organisms concerned.

TUBERCULOSIS[1]

The tubercle bacillus (*Mycobacterium tuberculosis*) can, as a rule, be demonstrated in the various foci of the disease, and, at one time or other in the development of the lesion, it is present in an active condition. The number of organisms in any given infected area even in the same lung varies considerably; and, in some of the chronic lesions, the organism, although probably in many cases still present, may not be demonstrable by ordinary staining methods. Tuberculosis in the human subject may be caused either by the type of bacillus most commonly found in the pulmonary forms of the disease in man—the **human bacillus**: or by that found in the disease in cattle—the **bovine bacillus.** Experimental evidence also shows conclusively that many animals, both domestic and wild, can be infected by means of either form.[1] The organism gains entrance to the body by various means. Probably the commonest is by inhalation of bacilli, derived from any source, *e.g.*, from dust containing the dried sputum of tuberculous patients: from the air in the immediate neighbourhood of tuberculous patients, which has become infected during a fit of coughing (the "droplet-method"): and by the introduction of bacilli into the mouth by hands or food contaminated by contact with infected sputum or other tuberculous material. The organisms may pass directly to the trachea, larger bronchi, or lungs, or they may be arrested by the moist surfaces of the tonsils or other adenoid tissue of the nasopharynx, and may then infect neighbouring lymph-nodes. In children, the primary infection of lymphatic tissue is commoner than is direct infection of the lung. The tonsils and the lymphoid tissue of the pharynx may be affected, but commoner

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[1] For brevity in description the characteristic nodular lesions of tuberculosis are called " tubercles." So general is the usage that, when otherwise unmodified, " tuberculosis " is understood when reference is made to " tubercles." When nodular formations are encountered in connection with *other* chronic infective granulomata, such must be specifically named, as, for example, " tubercul*ar* leprosy." The adjective " tubercul*ous* " is to be used as pertaining to tuberculosis ; while " tubercul*ar* " is employed to denote the state of being nodular, or of having tubercles without reference to ætiology. Thus urine can never be " tubercul*ar* " and the propriety of applying the adjective " tubercul*ous* " to urine, is doubtful. With regard to the derivation of the word, see footnote on p. 1134. The word " tubercle," from Latin *tuberculum*, diminutive of *tuber*, therefore means a small tuber or swelling, a small knob on a root, hence a term used to describe the granulomatous nodules of " tuberculosis."

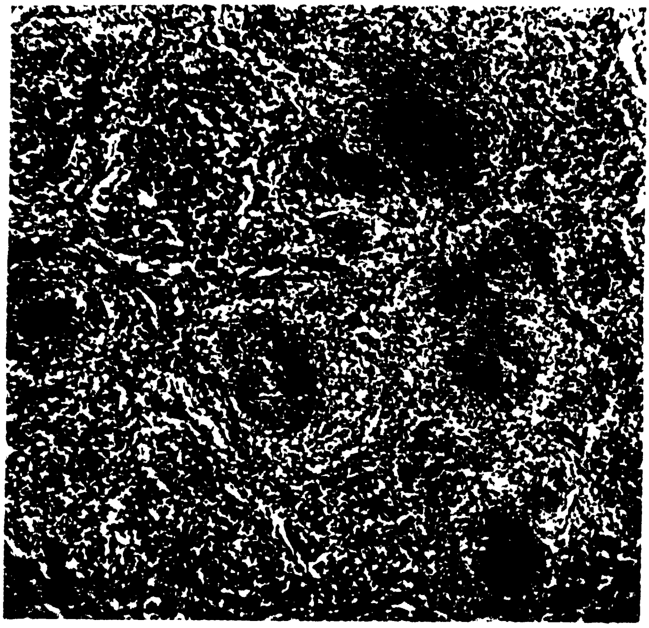

FIG. 29. Lymph-node, showing tubercle-follicles with caseation and giant-cells. × 50.

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[1] An acid-fast bacillus—"acid-*proof*" is a more accurate term—causing epidemics amongst *voles* is believed by Wells and Brooke (*Brit. Jour. of Exper. Path.*, 1940, **21**, 104, and *Brit. Med. Jour.*, 1940, *ii*, 261) to be distinct from, but allied to, the human and bovine types of tubercle bacilli and to have important immunological possibilities in relation to human tuberculosis.

sites are the intestines and the mesenteric lymph-nodes. The stomach is rarely involved, though the gastric juice does not kill the organism. The bacilli may pass directly through the wall of the small or large intestine; and the mesenteric lymph-nodes may become tuberculous without the coats of the intestine being obviously affected (p. 68). In this way, many of the cases of tabes mesenterica in children, in which there is no visible evidence of ulceration of the intestine, are to be explained, as are also some of those in young adults where the primary site of infection is apparently the lymph-nodes in the neighbourhood of the cæcum—the bacilli passing directly through the intestinal wall. In other cases, the walls of the intestine show ulceration in a more or less marked degree. As noted above, the infection of the intestine and mesenteric lymph-nodes is common in young children, especially in those who have been fed on cows' milk ; and, in such, the bovine bacillus can be demonstrated. Intestinal tuberculosis may occur also as the result of the swallowing of their infected sputum by patients suffering from the pulmonary form of the disease.

Invasion through abrasions or wounds of the skin is not common, though lupus may arise in this way ; and infection of the hands of pathologists or others working with tuberculous material may result in the production of "post-mortem warts."

There are many cases of the disease, especially in bone or in the brain, where the route of infection is not obvious. In some of these, there is probably a spread from the lymph-nodes by means of lymphatics ; but, in others, the blood-stream must be regarded as the means by which the bacilli are carried to various parts. This is the case especially in some affections of bones and joints, in meningitis and in tuberculosis of the testicle ; and, in such cases, there is often some local cause determining the site of attack, *e.g.*, previous injury or weakness. Where infection is transmitted from mother to child, the bacillus obtains access to the latter either by one or other of the methods already described, by the mother's milk, or—probably exceptionally—by direct transmission through the placenta. The child of a tuberculous mother may be of low vitality and, consequently, more susceptible to infection by the bacillus of tuberculosis than the child of a healthy mother ; but there is no evidence in the great majority of cases that the child is infected *in utero*.

Extension of Tuberculosis in the Body. A focus of tuberculosis, once established, has a tendency to spread indefinitely, though, associated with the spread, there is commonly a process of repair taking place, and "healing," or partial "healing," may occur. This spread may be by a direct infiltration of the surrounding tissues, by passage to various parts along the lymphatics, even in a direction opposite to that of the lymph-flow (retrograde infection), along air-passages or other natural channels, along surfaces, and by way of the walls of the blood-vessels or by the blood-stream. Thus, tuberculous disease of the lung is frequently associated with tuberculosis of the bronchi, trachea, or larynx, and the extension into the lung may be along these passages. This spread along natural passages is illustrated in certain cases of genito-urinary tuberculosis, where the disease, starting in the epididymis, may extend the whole length of the vas deferens to the vesiculæ seminales and the urinary bladder, and sometimes up the ureter to the kidney (Fig. 41, p. 73). The extension, however, both into the lung and into the kidney, may be by way of the lymphatics which surround these natural passages, and not along the lumen of the passages themselves. The extension along, or rather, in, the superficial skin- or mucous tissues is seen in lupus and in tuberculous ulceration of the intestine.

The pleura, pericardium and peritoneum may be the seat of widespread infection from fluid containing living tubercle bacilli which has accumulated in the cavities lined by these membranes. A similar miliary tuberculosis may occur in the bladder from contact with urine containing tubercle bacilli.

Spread by the blood-stream occurs when tuberculous foci invade and open into arteries or veins, or when the bacilli are carried by the lymphatics through the thoracic duct into the venous circulation. They may become lodged in the lungs and there produce acute miliary tuberculosis ; or they may pass through the capillaries of the lung and give rise to a generalised tuberculous infection. Portions of the infective material may become detached, and be carried in the blood to various organs or tissues ; or the spread may take place in the tissues of the walls of the vessels, and more especially along the perivascular lymphatics.

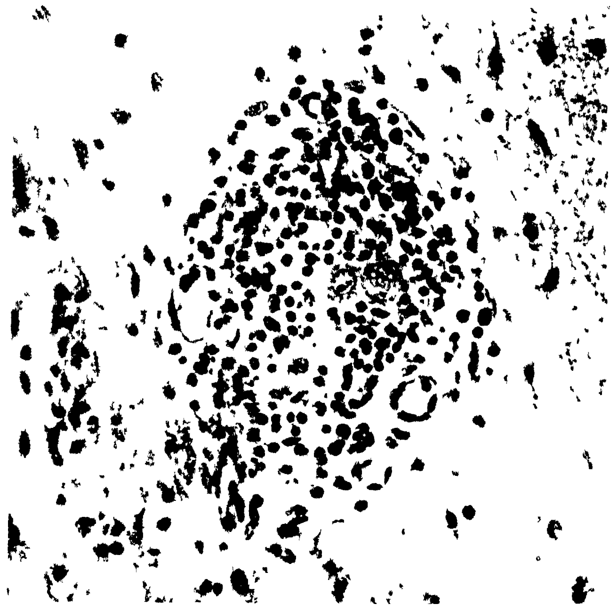

FIG 30 Early tubercle-nodule from knee joint, showing endothelioid cells and lymphocytes. × 300.

The Effects Produced by the Introduction of the Tubercle Bacillus, or of Material containing it, into Susceptible Animals. These effects can be studied by injecting the bacilli into the subcutaneous tissues, the peritoneal cavity, the anterior chamber of the eye, or through a mesenteric vein into the liver. The changes are practically identical in whatever focus the bacilli become lodged, and in our description we choose the peritoneum as a situation in which the pathological results can be traced without difficulty.

A preliminary polymorphonuclear-leucocyte emigration, lasting about two days, takes place ; and, though bacilli may be found englobed by these cells, the most actively phagocytic cells do not appear till a later period. These are mononuclear cells, which are found free in the peritoneal fluid in considerable numbers from the third day onwards, and persist till the death of the animal. They may contain large numbers of ingested bacilli. If the omentum be examined, the bacilli are found lodged in separate foci ; and, at these points, even in twenty-four hours, mitosis and proliferation of the fixed cells are seen. This proliferation increases, and, in from three to five days, there is a distinct cellular zone surrounding the bacilli. These cells are rounded or ovoid, with a vesicular nucleus and abundant cytoplasm. The origin of these cells, often called " endothelioid " cells, has been much debated, but the general view is that they arise from either fixed or mobilised cells of the histiocyte-series, including endothelial cells. By intravital staining, they give the reactions of the reticulo-endothelial series of cells. In them, the bacilli may be found, often in such numbers as to suggest a local multiplication within the cell-protoplasm.

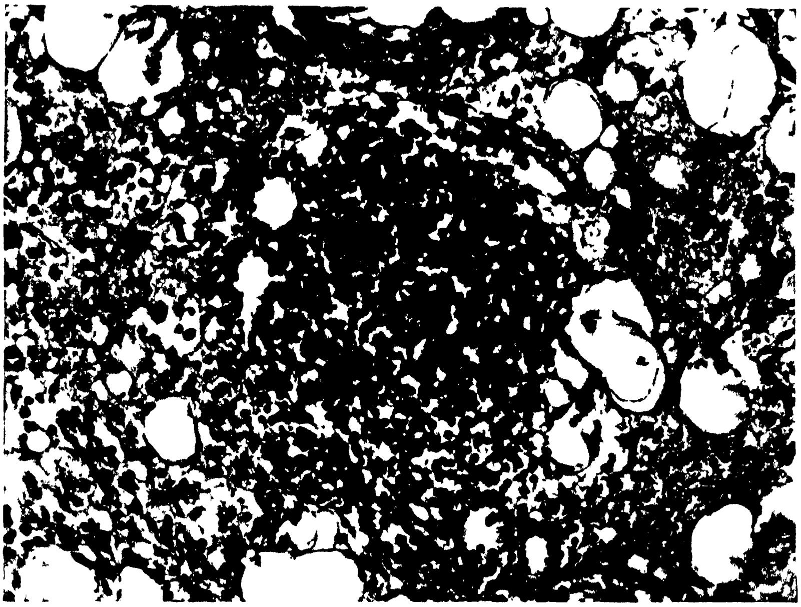

FIG. 31. Early tubercle-nodule from the omentum, showing loss of outline of central endothelioid cells (caseation). × 200.

In from six to ten days, these tubercle-follicles become surrounded by a zone of small round cells, each with a darkly staining nucleus which almost completely fills the cell. These lymphoid cells are derived partly by proliferation of local fixed cells, but great numbers of them migrate to the focus from the lymphatics and the blood-vessels. At this stage, the blood shows a distinct increase in lymphocytes. The relative numbers of endothelioid cells vary considerably in different cases and in different foci of the same case. In some, they may be scanty ; whilst, in others, the lymphoid zone may be scarcely evident. At this period, or usually somewhat later, *e.g.*, in from eleven to fifteen days, certain more or less important changes are seen in the follicles. The outlines of the endothelioid cells towards the centre of the follicle become

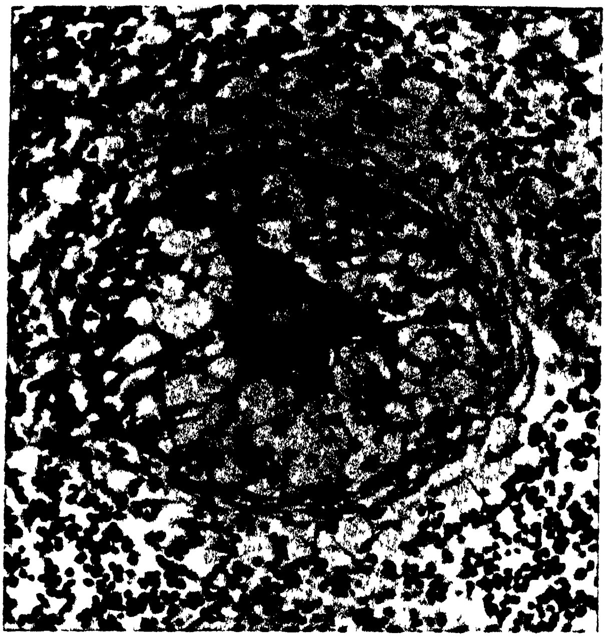

Fig. 32. "A giant-celled system," showing giant-cell with central caseation fibrous trabeculæ, and zone of lymphoid cells. × 200.

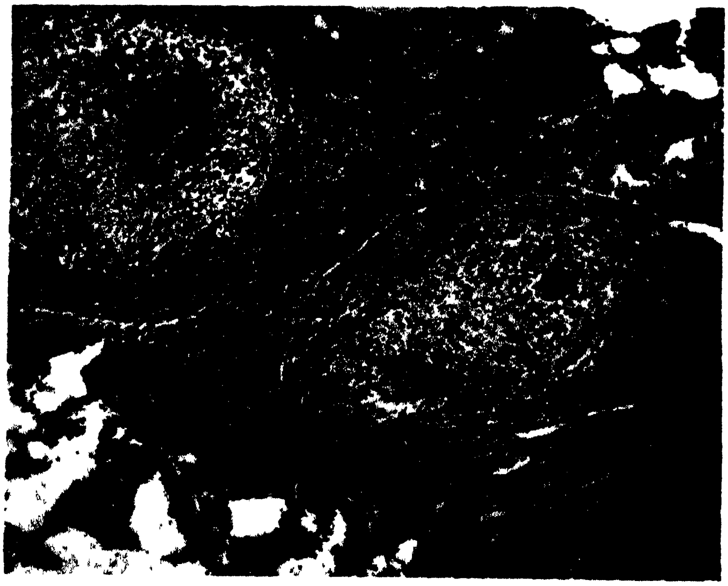

Fig. 33. Two coalescing chronic tuberculous nodules in the lung, showing central caseation, giant-cell formation, and peripheral fibrous-tissue overgrowth. × 75.

indistinct, the cytoplasm assumes a finely granular or "ground-glass" appearance, and the nuclei break up or become obscured. This process of caseation spreads from the centre to the periphery of the nodule ; and, in a short time, there is produced a somewhat granular focus, in which cell-outlines and nuclear staining are completely lost, and which is surrounded by a zone of lymphoid or proliferated connective-tissue cells. In this caseous centre, bacilli are usually demonstrable. In certain foci, and especially in those more slowly produced, large cells of irregular outline and having numerous nuclei, either scattered throughout the cell or arranged around the periphery, are seen. These are the giant-cells, and their cytoplasm presents the same granular or ground-glass appearance as is seen in the central caseous mass. Bacilli may be found in these cells also (Fig. 599, D., p. 997). Various views as to the mode of formation of these giant-cells have been propounded ; but most work on the subject seems to indicate that they are formed either by a fusion of the endothelioid cells or by the continued growth of an individual cell without any corresponding division of its cytoplasm, but with multiplication of its nuclei.

The degenerative changes and caseation in the nodules are due largely to the action of the toxic products formed during the growth of the bacilli ; though, no doubt, the absence of vessels, which have become obliterated during the process—probably by the swelling and degeneration of their endothelial lining—plays some part. Progressively larger areas are formed by fusion of these smaller lesions, the central part often breaks down and liquefies, and may become discharged, irregular cavities being thus formed.

Commonly, especially in the more chronic cases, a proliferative process of the nature of fibrous overgrowth takes place in the neighbourhood of the nodules. At first, the proliferative changes are evidenced by the presence of highly vascular granulation-tissue, which shows great numbers of large mononucleated wandering cells and giant-cells. This tuberculous granulation-tissue may undergo coagulative necrosis or caseation, but, in the chronic cases, it forms dense fibrous tissue. In this way widespread interstitial changes are produced; the focus of tuberculosis may be surrounded and completely shut in by this fibrous tissue, and become invaded by the newly-formed tissue, a nodule of fibrous tissue being eventually the sole representative of the original tuberculous focus. Often, however, caseous or calcareous material is found in this fibrous nodule ; and, microscopically, giant-cells may be seen.

These effects may be summarised thus :—

1. Reactive changes in and around the site of lodgment of the bacilli produce focal cellular areas which may be numerous and widespread throughout the body, giving rise to the condition of acute miliary tuberculosis. In some instances the process is slow and localised, with the production of granulation-tissue in which giant-cells are found. These more chronic tubercle-follicles or granulomatous masses may show, in and around them, fibrous tissue in various stages of growth.

2. Degenerative and necrotic changes in these masses—caseation—due in part to the local action of the bacilli and their products of growth.

3. General diffusion of the toxins, producing fever and wasting, and also fatty and amyloid degenerations, etc.

4. Proliferation in the neighbourhood of, and extending from, the local areas of tuberculosis—the result of the earlier reaction. The ratio between this and the destructive processes is an index of the relative activity of the

bacillus and of the vitality and power of resistance of the tissues. Thus, if the tissues are able to resist the action of the bacillus, either by virtue of their own vitality or through the feebleness of the bacillus, the proliferation will be in excess ; whereas, if the bacillus is virulent, or the tissues feeble, the destructive changes will predominate.

The resistance to the spread of the lesion is lower in children than in adults, and therefore the acute forms of the infection—acute miliary tuberculosis, tuberculous meningitis, tuberculosis in joints—are the usual manifestations in the young: whereas, in older patients, slowly progressive lesions are commoner. Sometimes, in the early stages of the acute forms of the disease, a fibrinous exudate with polymorphonuclear cells is present, and the caseous areas appear at a later period. This is seen in some cases of tuberculous meningitis, peritonitis, pericarditis or pleurisy.

The reactive foci are, at first, very small, rounded or irregular, opaque greyish-white in appearance and localised: or, as in the condition of acute miliary tuberculosis, widely diffused. These areas may, by individual increase in size, or by coalescence, come to form large tumour-like masses, as is seen sometimes in the brain. These larger areas have very often a yellowish or slightly greenish-yellow appearance, and may show softening or the formation of irregular cavities. Some of the more chronic nodules are pearly-white in appearance and very firm, owing to interstitial fibrous overgrowth. Others may show a deposit of lime-salts.

From the foregoing description, it is clear that the lesions produced by the introduction of the tubercle bacillus into the tissues are not by any means uniform, not only in different cases, but in different areas of the same case. The channel of introduction is also of importance in determining the character and distribution of the tuberculous lesions. They may be in the form of **acute miliary tuberculosis, caseous tuberculosis** or **fibroid tuberculosis**.

Acute Miliary Tuberculosis [1] (p. 553, and Figs. 332–3, pp. 554–5). This may be local, confined to some particular organ or tissue such as the lung ; or it may be general, every organ of the body being studded with minute greyish tubercle-granulations. It is commoner in children than in adults. In the majority of cases the bacilli enter the blood-stream as a result of the breaking-down of a tuberculous nodule in the wall of a vessel or by extension into the vessel of a caseous area in a neighbouring lymph-node. If the primary focus is in close connection with the pulmonary arteries or if the bacilli pass by the lymphatics and the thoracic duct into the venous system, they may be arrested in the lungs and produce the localised form. On the other hand, they may pass through the lung-capillaries and produce a general miliary tuberculosis. By eroding into other veins or arteries, the bacilli, liberated from the primary tuberculous focus, may be distributed widely, and innumerable small tubercles formed throughout the organs. In acute tuberculous meningitis (p. 992), bacilli from elsewhere may, by way of the blood-stream, produce localised foci in the brain, especially in the membranes or the choroid plexuses, and later, from these foci, the bacilli may be desseminated in the cerebrospinal fluid, producing a miliary tuberculous meningitis (pp. 992–8). In these miliary tubercles the cellular infiltration and proliferation described on pp. 58 to 61 are the prominent features. A certain amount of central caseation is usually present, but giant-cell formation and fibrosis are absent in most cases.

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[1] For the precise meaning of the word " miliary," *see* footnote on p. 1038.

Caseous Tuberculosis (p. 249, and Figs. 338–9, p. 559). In the lungs, this may be an acute condition with widespread caseation (caseous pneumonia); but, more commonly, the caseous tuberculosis seen in various situations in the body is a less acute process in which the necrotic action is pronounced. Areas of caseation varying considerably in size, frequently showing giant-cells and a moderate degree of fibrosis, are seen in the lymph-nodes, spleen, kidneys, genital organs (especially the epididymis), suprarenals, bones, brain, etc. The lesions may be firm, but usually they are soft and putty-like in consistence, or even semi-fluid. The firm, so-called "tuberculomas" of the brain and the soft semi-fluid caseous pus ("cold abscesses") of tuberculous infections of bone are examples of these two contrasted conditions.

Fibroid Tuberculosis. If the development of the tuberculous focus is slow and the lesion localised, fibrous tissue is developed both around and in the site of infection, and this newly-formed fibrous tissue may extend widely into the surrounding tissue. These changes occur in the lungs, and typical examples of this fibroid condition may be seen in cases of chronic phthisis (Figs. 339 and 341, pp. 559 and 561). Caseation is often present and giant-cells are usually numerous. Calcification may also be a feature of this condition.

This **diversity in the lesions** depends on **the resistance of the host, the number and virulence of the bacilli** introduced, and on **the allergic response** (p. 135) of the tissues. In the young child, infection takes place more readily than in the adult, and the lesion in the child is active, unrestricted in its spread and often has a fatal termination. In the adolescent, there is some tendency to limitation, for the progress is slower than in the child and the spread is often by the infection of bones, joints, etc. In the adult, the lesion is often more chronic, and varying degrees of fibrosis occur. This increase of resistance as age advances is usually attributed to a relative immunity produced by a mild infection or series of infections—so-called "sub-infection" or "sub-clinical" infection—during early life; though, in some cases, a natural immunity appears to be present. In the non-immune, *e.g.*, in previously non-infected native races, the introduction of tuberculous cases may give rise to a type of infection which is rapid and unrestricted in its spread amongst the population. In the individual, a few scattered bacilli in the tissues may not produce any appreciable destruction of these tissues, and the organisms themselves may be destroyed; whereas greater numbers of bacilli will produce considerable cellular reaction, a further and more rapid invasion and a local or a generalised infection. The effect of the **virulence** of the organism is more difficult to assess. One particular strain of the bacilli will invade the tissues of certain animals and not those of other animals. The human type, for example, can produce a rapidly spreading general tuberculosis in the guineapig, but at most only a localised infection at the site of inoculation in the rabbit, whereas the bovine type produces general tuberculosis in both the guineapig and the rabbit. Again, the human type is usually the cause of pulmonary tuberculosis, especially in adults ; but the bovine type is commoner, especially in children, in cases of infection of the intestine, lymph-nodes and bones. This difference in reaction seems, however, to be one of adaptability of the host rather than of virulence of the bacilli. Moreover, resistance is produced to a much greater degree by the inoculation of living bacilli in a non-virulent form (the so-called " **B.C.G.** " or *Bacille Calmette-Guérin*) than by the introduction of dead organisms. Calmette claims that he has produced a lasting immunity in children by introducing non-virulent living bacilli into the stomach with food. **Hypersensitiveness** of the tissues shown by patients (or animals), suffering from certain diseases, to the products of the organisms with which they have been sensitised (*e.g.*, tuberculin), is important in connection with tuberculous infection, invasion and spread, but its actual bearing on the problem of the diversity of lesions is not clear. If living bacilli, dead bacilli or bacterial products (tuberculin) are inoculated into an animal sensitised by a previous inoculation or infection, an **allergic response** (p. 135 *et seq.*) follows. The tissues at the site of inoculation undergo necrosis and caseation, but there is, as a rule, no evidence that the infection has produced pathological changes elsewhere. If living bacilli have been injected, they may undergo death and disintegration. It is claimed that the caseation at the site of inoculation is wholly an allergic reaction. If the same procedure is carried out in an animal free from tuberculosis, not only does the local lesion develop, but this is followed by the typical lymphatic spread to the neighbouring lymph-nodes and, later, to more remote tissues and organs. There is no localisation or allergic response, and the latter may therefore be regarded as a state of partial immunity and increased sensitivity. In cases of chronic tuberculosis, an absorption of successive minute amounts of the products of the growth of the tubercle bacillus over long periods produces this **sensitised** condition and therefore an injection of tuberculin may produce a definite allergic reaction. At the same time it must be remembered that this reaction is only a stage in the production of immunity—that the patient is not immunised, and a re-infection may produce a rapidly-spreading and fatal tuberculosis. The acute caseous nodules of young children (p. 552) are regarded as serious affections, for, though the child has become sensitised, its immunity has not had time to develop, the caseous nodule breaks down, possibly into a blood-vessel, and, there being either no or insufficient antibodies to prevent invasion, general tuberculosis may be produced.

TUBERCULOSIS OF SEROUS MEMBRANES—PERITONEUM—PLEURA—PERICARDIUM

The reactions which follow the introduction of the bacillus of tuberculosis into the peritoneal cavity are described on p. 58, and similar reactions, with slight variations, take place in the pleural cavities and pericardial sac. Tubercle-nodules, varying in size—very small in the more acute conditions and comparatively large in the chronic lesions—are formed in the peritoneum and pleura and to a less extent in the pericardium. The tuberculous process is not infrequently accompanied by more acute inflammatory changes and the deposit of fibrin, which may obscure the tuberculous nodules. When visible, the nodules are greyish or yellowish—depending on the degree of caseation which is present. In these serous cavities, the inflammatory changes bring about accumulations of fluid which may be serous, sero-purulent or purulent, and, in very acute cases, hæmorrhagic. The cellular content of the fluid is considerably increased, particularly in the lymphocytic type of cells. There may be present also, especially in the early stage, some polymorphonuclear leucocytes. Very commonly, adhesions are formed between the apposed surfaces of the serous membranes, and considerable infiltration of the membranes themselves may take place.

In the **peritoneum,** the great omentum may be so infiltrated, thickened, and retracted, that it measures an inch or more in its antero-posterior thickness—forming a characteristic cake-like mass towards the upper part of the abdomen. Tuberculosis of the peritoneum is commonest in children, but may occur at any age. It is usually secondary to tuberculosis of the lymph-nodes or of some abdominal viscus. The most frequent sources are tuberculosis of the mesenteric or retroperitoneal lymph-nodes, and of the ovaries and uterine (Fallopian) tubes. Intestinal tuberculosis rarely gives rise to a general peritoneal infection—only localised patches on the outer wall of the bowel, corresponding in their position with the ulcers in its interior, being, as a rule, affected. A similar localisation sometimes occurs in tuberculosis of the uterine tubes. Spread of a tuberculous infection through the diaphragm from the pleura may occur ; and, in rare instances, tuberculosis of the vertebræ and tuberculosis of the appendix are sources of infection. Tuberculous peritonitis is sometimes part of a generalised acute miliary infection. Adhesions formed between the coils of the intestine often give rise to serious obstruction. When chronic, calcareous deposits may be found in the adhesions and in the infected lymph-nodes.

In the **pericardium,** only in exceptional cases are the miliary tubercles numerous, and even these may be obscured by the fibrinous exudate which is usually present. Further, caseation takes place in this exudate, with considerable thickening of the pericardial layers, and sometimes calcification. The condition is generally secondary to a tuberculosis of the mediastinal lymph-nodes, but may occur also as a result of a tuberculous pleurisy or empyema, or be secondary to tuberculosis of the lung, sternum or ribs.

In the **pleura,** the condition is commonly secondary to disease of the lung or of the ribs or vertebræ. In the early stages of the disease, tubercles are formed on the visceral pleura and effusion into the pleural sac occurs. The fluid is at first clear, the cellular content mainly lymphocytic and the bacilli difficult to demonstrate. Possibly in many cases they are confined to the nodules and are not free in the fluid. The fluid may become hæmorrhagic. In some cases, especially in children, streptococci or pneumococci may also be present and the exudate may then be rich in polymorphonuclear cells. A common sequel is adhesion between the visceral and parietal layers at localised areas, especially over the apices of the lungs, or frequently extending over the whole surface, with thickening of the layers, caseation and even calcification.

TUBERCULOSIS OF THE CENTRAL NERVOUS SYSTEM. This subject is dealt with under Neurotuberculosis or Tuberculosis of the Central Nervous System (pp. 992 to 1000).

TUBERCULOSIS OF BONES AND JOINTS. In these common manifestations of tuberculous disease, the infecting bacilli—usually of the bovine type—are carried in the blood-stream or possibly, in some cases, by the lymph, and become lodged either in the periosteum or in the bone, and rarely in the synovial membrane. Spread may occur secondarily from affected joints; but frequently, in tuberculosis of joints, the bone adjoining the articulation —the epiphysis or the diaphysis—is first affected. Cellular proliferation takes place at the seat of lodgment of the bacilli, and definite tubercle-nodules are produced. These nodules show giant-celled systems, and, as these increase in size and undergo caseation, the bony trabeculæ become gradually absorbed. **Necrosis** of the bone frequently occurs, the necrosed portion becoming separated, and lying in a cavity which has softened caseous walls. The necrosed portions or **sequestra** may be small; but they may be large and rarefied where the lesion is an acute infiltrating one: or dense and sclerotic where the necrosis has taken place because of interference with the circulation. **Caries** is a more frequent result of the tuberculous process. In the vertebral column this lesion may be limited to one vertebral body, or it may affect several. Occasionally, it commences in the transverse process and spreads to the vertebral body. It is found at any part of the spinal column, but is of most frequent occurrence in the lower thoracic and upper lumbar regions. The tuberculous infection, after destroying the anterior common ligament, reaches the dura, the outer surface of which becomes thickened and infiltrated. The tubercle-granulations extend into the substance of the dura, and, at a later period, give rise to extensive tuberculous infiltration of its inner surface.

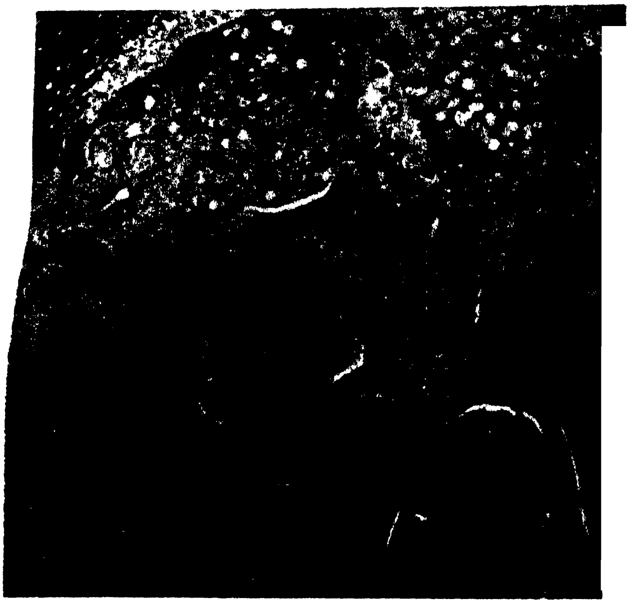
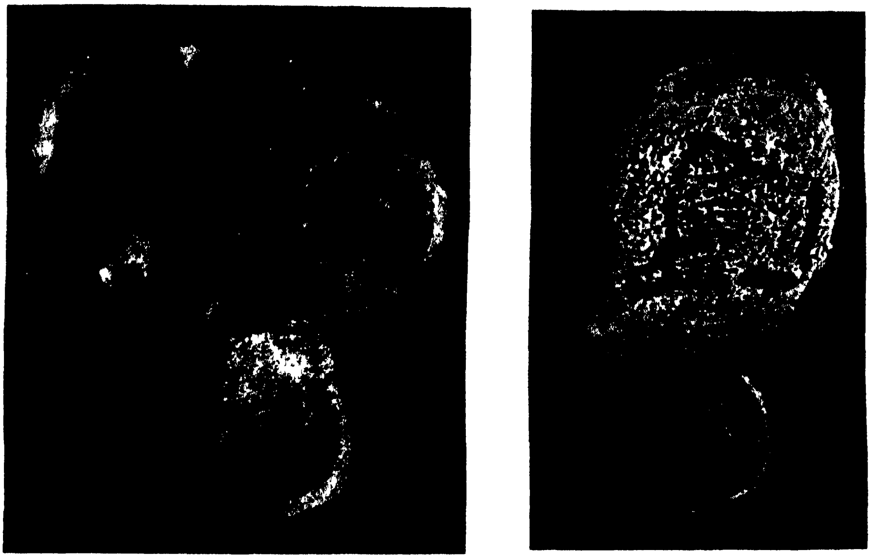


FIG. 34. Tuberculosis of the os magnum, showing cellular proliferation, with tubercle-follicles (left, lower part), caseation, and absorption of bone. × 28.

Further extension takes place, and the pia-arachnoid and various nerve-roots become involved. On account of the extension of the tuberculous reaction in the canal and the increase in caseation, compression of the spinal cord (*see* Fig. 600, p. 999), with consequent ascending and descending degenerations, may follow. By reason of the destruction of the vertebral bodies, curvature of the spine with displacement of, and pressure on, the spinal cord, takes place, and necrotic softening is produced. Death supervenes, in some cases, from sudden dislocation of the diseased vertebræ. This is the case especially where the odontoid process, or the transverse ligament which holds it in position, becomes eroded. In a proportion of cases, localised patches of softening or a complete transverse lesion of the spinal cord may occur apart from pressure. These results are due probably to interference with the blood-supply (ischæmia) from involvement of the nutrient vessels, and the obliteration of their lumen by the tuberculous process, or to the action of the toxins.



(A)

FIG. 35. Caries of the head of the tibia and articular surface of the patella. Macerated specimen from a case of tuberculosis.

(B)

Another similar specimen of the same showing sequestrum.

In the long bones, large portions become irregularly softened, eroded and absorbed, and the medullary cavities are lined with soft tuberculous granulation-tissue, or, more rarely, with caseous material. If the tuberculous infection spreads to the joint, the articular cartilages and the synovial membrane become invaded: pinkish, semi-caseous granulations are formed, with, at a later period, softening, erosion and ulceration : and the synovial membrane is converted into a soft, putty-like material. The ligaments and other tissues round the joint become transformed into œdematous tuberculous granulation-tissue. Though muscle itself is rarely affected primarily, extensive invasion from tuberculous foci in bones and joints is frequent, giving rise to abscesses or other destructive lesions in the muscle. The caries may lead to collapse of the affected bones, for example, the bodies of the vertebræ in Pott's disease of the spine (*see* Fig. 600, p. 999). Frequently, a process of necrotic softening resembling suppuration develops—the so-called **cold abscess**—the contents consisting of caseous debris, pus-cells, etc. This condition is seen in **lumbar or psoas-abscesses.** The tuberculous process may affect the periosteum either primarily or secondarily, and, if there is extensive infiltration, subperiosteal abscesses form, with necrosis of the underlying bone. The cancellous tissue is the favourite nidus for the commencement of the process ; but the earliest change is seen occasionally in the midst of dense bone. It is not uncommon to find extensive tuberculosis in the bone-marrow, which may also be affected as part of a general miliary tuberculosis (*see* pp. 664 and 668). The bones most commonly attacked are those rich in cancellous tissue, *e.g.*, the vertebræ, the bones of the hands and feet, and the ends of the long bones. The bones of the skull are not often involved, but tuberculosis of the temporal bone may occur secondarily to tuberculous disease of the middle ear ; or tuberculosis may implicate some of the bones at the base of the skull where the affection has spread upwards from the vertebral column.

The tuberculous process is accompanied by the ordinary phenomena of chronic inflammation, as well as by rarefaction, so that the surface of the bone is usually rough and shows irregular projections, the result of a formative periostitis. It is not uncommon, however, to find a tuberculous sinus surrounded by very dense bone. Similar proliferative formation of new bone occurs in tuberculous disease of joints ; and, in the healing of tuberculous foci in bones or joints, the formation of fibrous tissue may take place with calcification or even ossification, and in joints bony ankylosis may occur.

TUBERCULOSIS OF LYMPH-NODES. This condition of lymph-nodes may be acute or chronic, and infection may occur by way either of lymphatics or of blood-vessels—much more commonly by the former of these channels. In some instances, the tuberculosis of the lymph-nodes is primary. Thus, the mesenteric lymph-nodes may be infected by tubercle bacilli which have passed directly to them through the intestinal mucous membrane by way of the afferent lymphatic channels or lacteals (p. 57) ; or the cervical lymph-nodes may be similarly infected by organisms which pass through the tonsils or pharyngeal mucous membrane. Frequently, however, some catarrhal inflammation may be present and this aids the penetration of the bacilli through the mucous membrane, *e.g.*, of the intestine. In the case of the tonsils and pharyngeal lymphoid tissue, direct infection, with formation of giant-cell systems, occurs, and a certain proportion of cases of supposed primary tuberculosis of cervical nodes is undoubtedly due to secondary infection from the primary tuberculous lesions in these tissues.

Extension of the infection, due to the spread of the bacilli from some other focus of disease, is common, for example in the case of the bronchial and mediastinal lymph-nodes in tuberculous disease of the lungs ; though, in this connection, it should be mentioned that infection of the lung may be secondary to tuberculosis of the cervical, mediastinal, and bronchial lymph-nodes. Such secondary infections of the lymph-nodes are commonest in childhood and in early adult life, but may be found at any age. The lymph-nodes at the brim of the pelvis, especially towards the right iliac fossa, are often affected in young adults, infection occurring probably from the terminal part of the ileum and from the cæcum and commencement of the ascending colon. Infection of the mesenteric lymph-nodes—**tabes mesenterica**—has already been mentioned, and occurs principally in childhood, the chain of nodes at the ileo-cæcal junction being particularly liable to infection, though any or all the mesenteric lymph-nodes may be affected ; and, from them, the disease may spread to the retroperitoneal and other abdominal groups, and to the mediastinal, bronchial and other lymph-nodes.

To the naked eye, the affected lymph-nodes may show minute greyish-white nodules or larger yellowish-white caseous areas which may spread throughout the whole of the node. On microscopical examination, giant-cell systems may be abundant, or only a mass of caseous material with an occasional giant-cell at the periphery may be present. Sometimes marked proliferation of the reticulo-endothelial cells occurs, the nodes are enlarged and very cellular, and little or no caseation may be seen. Giant-cells, though often few in number, are usually present. Fibrosis and calcification may occur in any tuberculous lymph-node ; and, in those showing rapid caseation, necrotic softening—so-called "tuberculous" or "cold-abscess formation"—is not uncommon.

FIG. 36. Tuberculosis of retroperitoneal lymph-nodes around abdominal aorta.

Tuberculosis of lymph-nodes may remain localised for a long period, and gradual spontaneous recovery may take place ; but on the other hand the infection often reaches other nodes, and leads to widespread tuberculosis. Such extension may be either acute or chronic, and, in the latter case, it may be very gradual. Rows of tubercle-nodules are sometimes seen along the lines of the lymphatic vessels in the perivascular tissue, or in the wall of the thoracic duct. These may ulcerate into the vessels or the duct, and lead to the production of acute miliary tuberculosis.

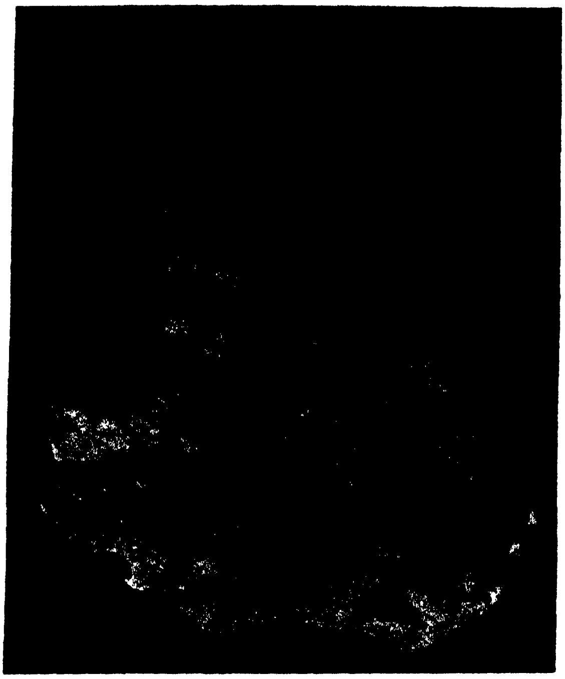


FIG. 37. Mass of tuberculous cervical lymph-nodes.

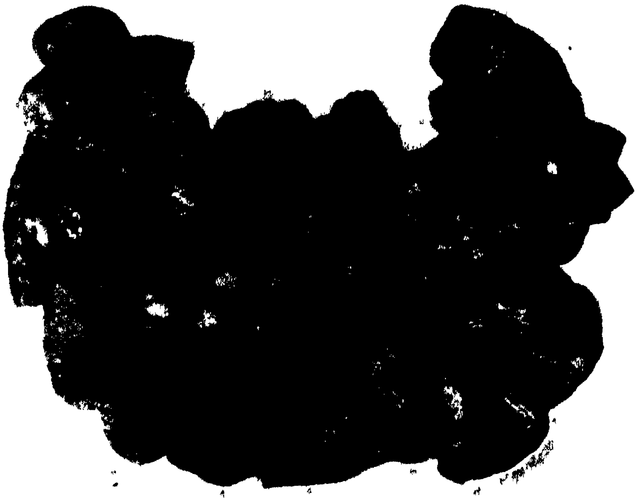


FIG. 38. Tuberculosis of mesenteric lymph-nodes in child (tabes mesenterica).

TUBERCULOSIS IN THE ALIMENTARY TRACT. Tuberculous infection is comparatively uncommon in the **mouth,** but lesions which sometimes simulate epithelioma may occur on the dorsum or at the margins of the **tongue,** and tuberculous nodules are sometimes found also at its root. Small nodular masses are formed, which undergo caseation, and in some cases ulceration. "Tuberculous papillomas" are usually masses of granulation-tissue formed in connection with fissures of the tongue, subsequently infected with tubercle bacilli. Lupus of the face may spread so as to involve the mouth and nose.

In some countries, and especially in certain localities and districts, tuberculosis of the **faucial tonsils** is relatively common, but it is recognised oftener in the routine histological examination of tonsils than as a clinical entity. It may occur as part of a generalised miliary tuberculosis, but frequently is due to direct invasion through the mucosa of one or more crypts.

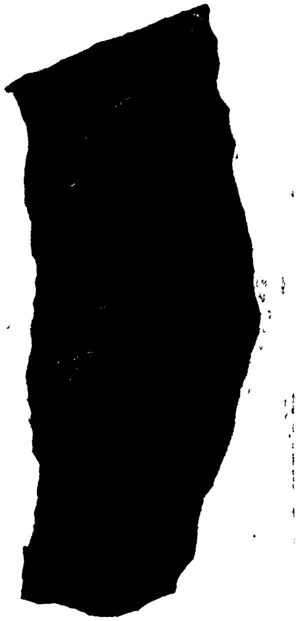


FIG. 39. Tuberculous ulceration of the intestine, showing the raised thickened edges and the irregular floors of the ulcers, and their tendency to spread transversely.

Tuberculous ulceration of the **stomach** is rare, and tuberculosis of the **intestine** in adults is generally secondary to pulmonary tuberculosis. In young children, however, the primary affection of the intestine is caused by the ingestion of milk or other food containing the bacilli, commonly the bovine type. The main seat of infection is the lower part of the ileum, where the Peyer's aggregated patches and the solitary lymph-follicles become swollen, either uniformly, or in scattered, irregular areas; but tuberculous foci also frequently occur in other parts of the submucous or mucous coats. These swollen patches, covered at first by mucous membrane, which may show catarrh, later undergo central caseous necrosis, and the mucous membrane over them sloughs, leading to the formation of small rounded ulcers which increase in size by coalescence. Both the floor and the edges of the ulcers are infiltrated and thickened, the floor appearing caseous, ragged, and granular, and the margin raised and irregular. The ulceration extends peripherally, and also more deeply into the bowel-wall, and, at its lateral edge, it tends to spread especially transversely in the intestinal mucosa beyond the margins of the Peyer's aggregated gland or solitary lymphoid follicle, if it has either of these as its site of origin, and it may ultimately completely encircle the bowel. In its further spread, it extends to the muscular and peritoneal coats, and produces, in the deeper parts of the serous coat, a number of tubercle-granulations (Figs. 40 and 420, p. 755)—often seen along the lines of the lacteals or other lymphatic channels, by which the process tends to spread. Thickening of the serous coat and adhesions to surrounding parts are thus produced, and, on the abdomen being opened, the situation of the ulcer in the intestine can often be detected by the presence on the peritoneal surface of these thickened, inflamed areas, in which whitish or greyish tubercle-granulations are studded. Overgrowth of fibrous tissue sometimes leads to contraction and narrowing of the ulcerated area. These tuberculous strictures may be multiple. On account of this thickening, perforation seldom occurs, but in certain acute cases the ulcer may perforate before such protective thickening has had time to develop. In such acute cases, the edges are usually ragged and undermined, and the floor is not infiltrated to any appreciable degree—the appearances resembling those of typhoid, rather than of typical tuberculous, ulceration. The surrounding mucous membrane often shows catarrh and congestion, which may be very intense. On microscopical examination, the nature of the lesion is detected by the presence of tubercle-follicles, caseation, and the causal bacilli.

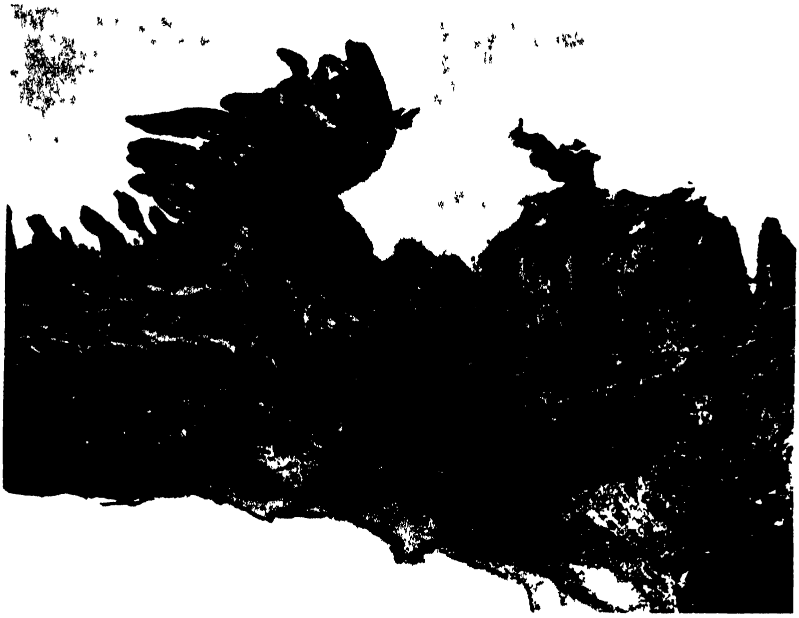


FIG. 40. Tuberculous ulceration of the intestine, showing the raised, undermined edge, the tubercle follicles, and especially the great thickening of the serous coat. × 16.

The cæcum and **large intestine** are affected less frequently than the small intestine by the tuberculous process; and the ulcers, when they do occur in these regions, tend to be of the acute type and to spread widely, with the production of large irregular areas of destruction of the mucous membrane. Chronic ileo-cæcal tuberculosis also occasionally occurs, and may lead to the formation of fibrous thickening, with symptoms of obstruction simulating the effects of malignant disease ; but many of the cases diagnosed in the past as "tuberculous" have undoubtedly been examples of "non-specific granulomatous regional ileitis," "regional enteritis" or "Crohn's disease" (p. 743). The **rectum** rarely shows tuberculous ulceration ; but, apart from cases of **fistula-in-ano** secondary to pulmonary tuberculosis, which *are* likely to be tuberculous, many instances of fistula, in the past diagnosed as "tuberculous," have in reality been complications of regional ileitis or of ulcerative colitis (p. 755).

GENITO-URINARY TUBERCULOSIS (pp. 885 and 907). Tubercle-granulations, varying in number and size, are frequently present in the kidney, especially in the cortex and along the lines of the interlobular vessels, in general miliary tuberculosis and sometimes in chronic tuberculosis of the lungs or lymph-nodes; but the most serious tuberculous lesion of the kidney itself is "**renal phthisis**" which is usually part of a widespread **genito-urinary tuberculosis,** a condition often, but by no means invariably, associated with the presence of tuberculous lesions elsewhere, for example in the lungs and pleuræ. The primary focus may occur in the kidney-substance itself from bacilli deposited there from the blood-stream; or in the female it may arise from a preceding affection of the uterine tube. It is commoner in the male, and frequently is first recognised clinically in the globus major of the epididymis, the body of the testicle and the vas deferens (pp. 57-8). By way of the latter—usually along its lymphatics—the process spreads to the seminal vesicles, urethra and bladder, and up the ureters to the renal pelves. In other cases again, the disease may—either from hæmatogenous or lymphatic infection, or by spread from a focus within the kidney—affect the submucous coat of the pelvis of one of the kidneys, from which position it spreads downwards, involving the ureter, bladder, etc. It may then extend upwards along the other ureter, and attack the kidney of the opposite side. *As evidence of the localisation of spread, the following*

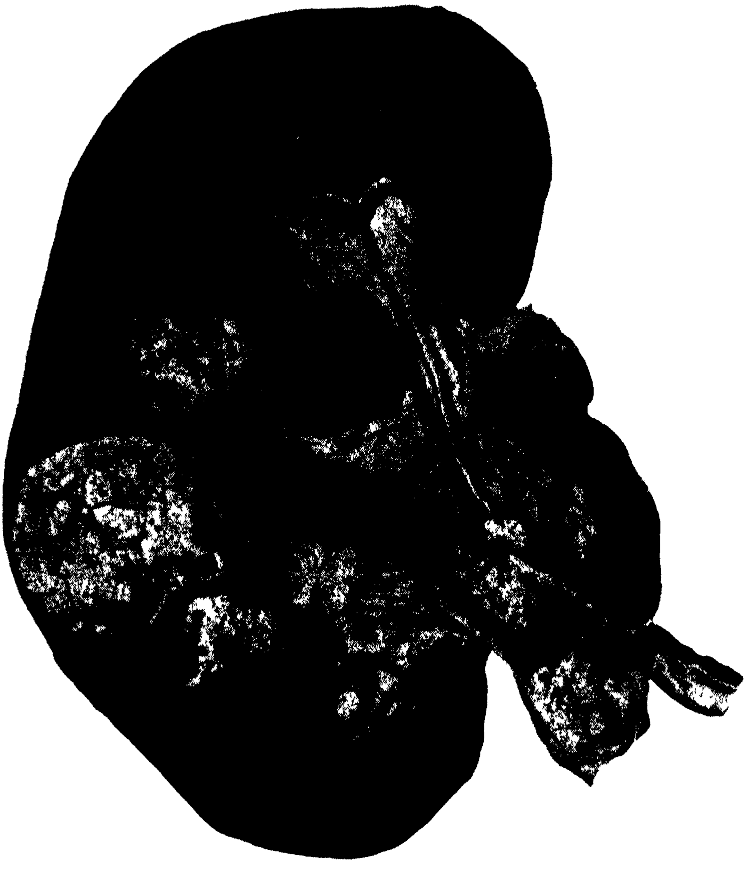


FIG. 41. Tuberculosis of the kidney, extending upwards from the bladder. There were two ureters. Note the tuberculous material in the one opened up, and the infection of the portion of the kidney drained by that ureter. The second ureter and the portion of kidney connected with it were not infected (*see* p. 885).

record is worthy of consideration (Fig. 41). A tuberculous affection of the left iliac bone had involved the kidney of the corresponding side. This kidney had two ureters with separate pelves in the kidney and each proceeding separately to the bladder (p. 852). One ureter was involved in the tuberculous process and was thickened and caseated throughout its whole extent from the bladder to its pelvis. This pelvis, with the portion of the kidney served by it, was extensively caseated. The other ureter was healthy, and the corresponding portion of kidney was unaffected. The opposite kidney and its ureter were unaffected. In this case, spread had undoubtedly been by, and was limited to, one of the two ureters of the left kidney. The second ureter acted as a control in this unusual human "experiment." By whichever method the disease reaches the renal pelvis, it speedily attacks the mucous membrane, especially of the calices immediately around the papillæ, where caseating ulcers are formed, surrounding which there is a zone of intense congestion. These ulcers gradually spread into the substance of the kidney, which may become converted either into a caseous mass or—if the ureter is partially or wholly obstructed by the tuberculous process—into a series of sacs and pouches with caseous walls

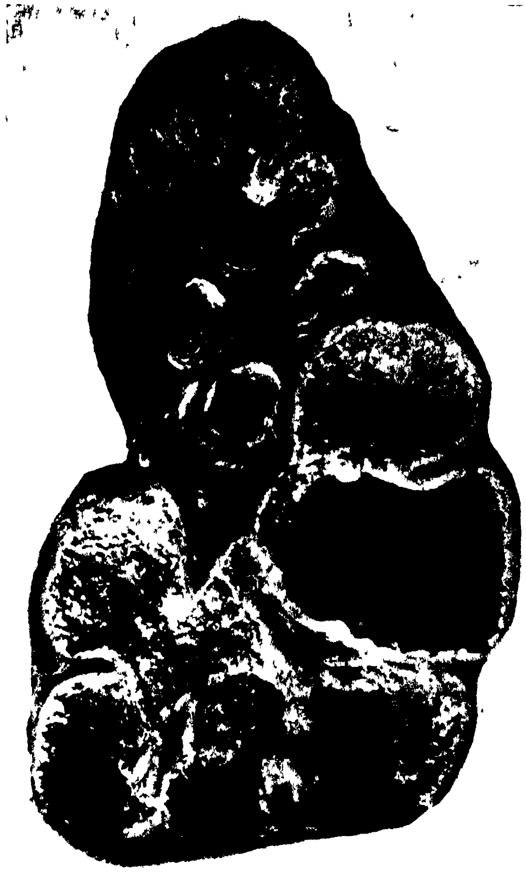


FIG. 42. Tuberculosis of kidney—" renal phthisis." The kidney-substance has been almost entirely replaced by large cyst-like cavities, which have resulted from the progressive ulceration and dilatation of the pelvis and its calices. The walls of these spaces are ragged and caseous.

and contents, corresponding to the dilated and ulcerated calices. The size of such a kidney varies with the degree of obstruction and the amount of distension produced, the organ being, in some instances, much enlarged. This enlargement, however, is not a constant feature—the kidney being sometimes normal, or even reduced, in size. In the substance of the kidney, beyond the line of ulceration, groups of tubercles may be found, but in some cases these are absent. There is usually an attempt to shut off the diseased area by the formation of a zone of fibrous tissue, as in tuberculous lesions elsewhere. Associated lesions in the kidney-tissue, such as acute nephritis, subacute diffuse and interstitial nephritis, and amyloid disease, may be present. Fibrous changes in the capsule and surrounding fatty tissue, with adhesions to neighbouring structures, are practically always found.

As a rule, when seen *post mortem*, both kidneys are affected, though perhaps in varying degree. Where one kidney only is diseased, the right organ is more frequently affected than the left. When the disease commences on one side, and extends to the bladder and up the opposite ureter, both ureters become swollen, thickened, and hard, and more or less filled with caseating material, causing a diminution in calibre or sometimes the complete blocking of one ureter. In the bladder, the infection produces cystitis, catarrhal changes, and perhaps extensive ulceration ; though, in some cases, the tuberculous lesions are localised, especially to the region of the trigone. In the epididymis, the tuberculous process, in addition to involving the vas deferens, may spread to the testis, usually, at first at all events, on one side only. The vesiculæ seminales may also become involved.

Results. Most commonly, genito-urinary tuberculosis is a steadily progessive disease leading to a fatal termination. In a few instances, however, the process may be arrested, the caseous material becoming inspissated and perhaps calcified, and surrounded by dense fibrous tissue corresponding with the capsule of the organ. Such instances of " healed " tuberculosis of the kidney may sometimes be found in the bodies of old persons, in whom the presence of genito-urinary tuberculosis had been unsuspected during life.

TUBERCULOSIS IN OTHER ORGANS AND TISSUES

1. **The Suprarenals.** In the suprarenals, small miliary tubercles may be found in general tuberculosis in children. In adults, lesions varying in size from small miliary nodules up to large caseous areas may be present. Such nodules if scattered do not necessarily cause any serious disorganisation of function ; but, when they coalesce and produce large areas which occupy the greater part of both glands, the function is sufficiently impaired to give rise to the increased pigmentation of the skin and mucous membranes and the other signs and symptoms of **Addison's disease** (pp. 842B–845). In this disease, when due to tuberculosis, both suprarenals are affected, though often in varying degree. There is extensive caseation and destruction of the glandular tissue, the organs being usually somewhat enlarged and irregular in shape. The caseous nodules are often surrounded by dense fibrous tissue due to chronic proliferative inflammatory changes producing adhesions to the surrounding fat. On section, they may be firm and fibrous, or softer and

more caseous. Fibroid bands may be found among the caseated debris, and the latter may undergo calcification.

Tuberculous disease of the suprarenals is not necessarily associated with tuberculous disease elsewhere, though tuberculous lesions are not infrequently found in other parts of the body, for example in the lungs, joints, spine, or lymph-nodes.

2. **The Thyroid, the Pancreas and the Salivary Glands.** In these organs, tuberculosis is rare. Miliary and solitary caseous nodules are seen sometimes in cases of generalised miliary tuberculosis, and the organs may become involved from neighbouring lymph-nodes.

3. **The Liver and Spleen.** Small miliary or larger caseous nodules occur, and in the spleen the latter may reach a quarter or a third of an inch (6 to 8 mm.) in diameter. These large nodules occur especially in children and are also found in the tuberculosis of monkeys in captivity ("ape-tuberculosis"). The infection is usually part of a general tuberculosis or due to an extension from a tuberculous area in the neighbourhood, *e.g.*, a localised tuberculosis of the peritoneum. In the liver, the larger caseous areas may soften and produce irregular cavities, the walls of which are often bile-stained. Obstruction of the bile-ducts by the spread of tuberculosis in the liver is very rare.

4. **The Mammary Gland.** Tuberculosis of the breast is not uncommon, and occurs as a secondary infection from a tuberculous focus in the adjacent tissues, *e.g.*, cervical lymph-nodes or a tuberculous rib ; but it may also be spread by the blood from more distant foci. The areas may become softened, infected with pyogenic organisms and produce irregular abscesses. Before softening and infection takes place, the condition is liable to be diagnosed clinically as carcinoma, and microscopical examination of a biopsy-specimen may be necessary to demonstrate the true nature of the lesion.

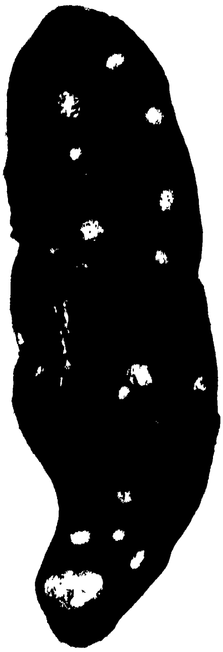


FIG. 43. Caseous tuberculous nodules in the spleen.

5. **The Heart and Blood-vessels.** Miliary or larger caseous nodules may occur in the heart in cases of acute general tuberculosis or be due to extension from neighbouring foci. In the endocardium, tuberculosis is rare, but in the myocardium there may be extensive invasion of the septum or the wall of the left ventricle and associated fibrosis. In the case of arteries and veins these become infected by extension from tuberculous areas in the lungs or from caseous lymph-nodes. The nodules in the walls of arteries, veins and lymphatics may erode into the lumen of the affected vessel, and the caseous material with the bacilli be carried by the blood or the lymph-stream and give rise to a general tuberculosis. The walls of the arteries may be weakened by the caseation, and aneurysmal dilatation result. Around the tuberculous areas, vascularity may be increased, though the vessels in the area are obliterated.

6. **The Upper Air-Passages.** Tuberculosis of the upper air-passages is commonly secondary to tuberculosis of the lungs. In the nose, it may arise as a local extension from lupus of the face. The lesion may appear in the form of localised tubercle-granulations, as minute shallow ulcers following these, or as widespread infiltration of the tissues accompanied by inflammatory œdema and secondary ulceration. Occasionally, the granulomatous overgrowth may simulate tumour-formation. The pharyngeal tonsil, when it is the seat of adenoid overgrowth due to, or complicated by, tuberculous infection, exhibits lesions similar in type to those found in the faucial tonsils (p. 71). Some writers have commented upon a possible relationship between tuberculosis of the adenoids and tuberculous otitis media. Tuberculosis of the pharyngeal lymphoid masses, however, is frequently observed without involvement of the middle ear or mastoid region. In the larynx, the small ulcers are usually near the margins of the vocal folds (cords) and on the posterior commissure; and, in more extensive infiltration, the ary-epiglottic folds and the epiglottis are swollen, thickened and ulcerated ("laryngeal phthisis"). In some cases, a perichondritis, especially of the thyroid cartilage, is seen.

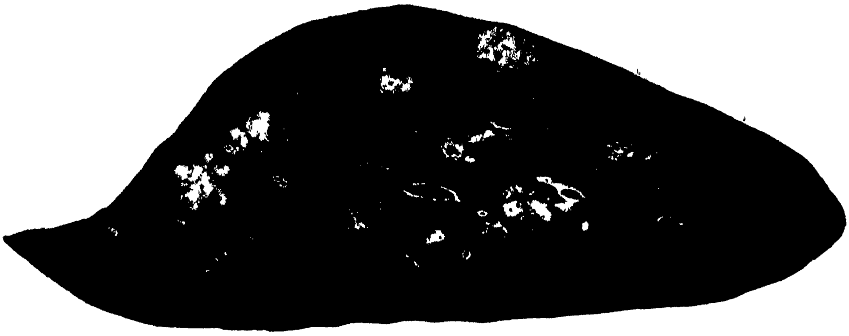


FIG. 44. Chronic tuberculous nodules in the liver.

7. **The Lungs.** *See under* Respiratory System, p. 550 *et seq.*

Tuberculosis in the Lower Animals. Tuberculosis is common and widespread amongst **cattle,** but may also affect, though to a less extent, **horses** and **pigs**; in fact, almost all warm-blooded animals are susceptible to the disease, and it is common especially in domesticated animals. The bacillus of human tuberculosis can infect most of these animals; and the organism of bovine tuberculosis, which has been regarded as a different type or variety, can, and often does, give rise to tuberculosis in the human subject. In cattle, the structures most frequently affected are the serous membranes—the pleura and peritoneum especially. In these positions, large bean-shaped or potato-like nodules are seen attached to the surface, or supported by membranous villous-like projections. They may form very large masses, and are usually white, firm and frequently calcareous. For tuberculosis in **voles,** see footnote on p. 56.

Avian tuberculosis is common in domesticated birds such as hens, pigeons and turkeys and also in pheasants. Geese and ducks seem to be immune. It is doubtful if this "avian" bacillus causes disease in man, though rare cases, believed to be due to it, have been recorded. Inspection of the livers of poultry may show scattered tubercles or large areas of confluent caseous necrosis.

Sarcoidosis of Boeck. Though this cannot be classed as a typical granuloma, its resemblance to tuberculosis justifies us in including a short description of the disease in this chapter. It is a disease of long duration with a tendency to spontaneous remissions and characterised by enlargement of the lymph-nodes and spleen, and, in some cases, infiltrations in the skin, lungs, bones, lacrimal glands and, more rarely, in the myocardium, endocardium, pancreas, and bone-marrow. Iridocyclitis is said to occur in 10 per cent. of cases.

The enlargement of the **lymph-nodes** may be general—slight in some nodes, considerable in others. The affected nodes are œdematous and, on microscopical examination, nodular areas, varying in number and composed of masses of proliferated reticulo-endothelial cells with occasional giant-cells of the "foreign-body" type, are observed. There is usually no caseation, and no evidence of active tuberculosis to be found even on careful microscopical search and animal-inoculation. Fibrosis, especially at the periphery of the nodules, is sometimes present. The spleen is enlarged, and the characteristic lesions may be scanty or even solitary and found only in the germinal centres.

In the **skin,** small papules may appear on the cheeks, forehead, extensor surfaces of the arms and the back of the legs; or larger nodules develop on the face and limbs. Immediately under the corium, the cellular changes described above are present.

In connection with the **lungs,** the lymph-nodes at the root or in the mediastinum may alone be involved, or there may be, throughout the lung-tissue, scattered nodules showing the characteristic cell-structure. Fibrosis is sometimes present to a considerable degree.

The lesions in bone are said to occur almost exclusively in the phalanges of the hands and feet. The involvement of the lacrimal glands is associated with a lesion on the skin of the eyelid. The characteristic cellular lesion has also been observed in the myocardium, endocardium, and bone-marrow. The blood may show a moderate degree of mononucleosis and in a few cases eosinophilia. Lesions resembling those of sarcoidosis have been found in patients with tuberculosis, syphilis, leprosy and leishmaniasis; but most observers regard sarcoidosis as a specific disease, possibly allied to lymphadenoma.

LEPROSY[1]

A bacillus closely resembling in many of its morphological characters the tubercle bacillus is found constantly, and often in enormous numbers, in the lesions of leprosy. This organism, described by Hansen in 1874, is regarded as specific, but, on account of the incubation-period of the disease lasting for months or years, it is difficult to establish absolute proof. Adler (1937) claims that, by the introduction of a fragment of a human lepra-nodule into a space between the skin and the fascia of a splenectomised Syrian hamster (*Cricetus auratus*), he was able to produce, not only a nodule at the site of inoculation, but lesions in the skin far removed from the site and that in these the bacilli were very numerous. He found them also in smears from the liver. In the Middle Ages,leprosy was a common disease throughout Europe, including Great Britain. The disease is now localised to certain districts, and is prevalent in Norway, India, China, Mexico, parts of South America, the Sandwich Islands, Egypt and Abyssinia. Formerly, in America, cases were fairly common among the Scandinavian settlers in the Great Lakes district; and sporadic examples are still found widely scattered, but practically always in foreign-born individuals who came, perhaps in childhood, from regions in which leprosy was prevalent.

The disease can, apparently, be transmitted from one person to another by prolonged and very close contact, and the part played by possible insect-vectors in its transmission is still an open question. Leprosy presents itself in two forms—the **tubercular** and the **anæsthetic.**

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[1] Greek λέπρα, *lepra,* leprosy, that which makes the skin scaly, from λεπίς, *lepis,* or λέπος, *lepos,* a scale, rind or husk.

Lepra Tuberculosa. In this variety, nodular projections are formed in the skin and subcutaneous tissues, especially of the face and hands, and in the mucous membranes of the mouth and larynx. On the face, the nodules are seen in the cheeks, nose, ears and brow. The eyebrows and eyelashes fall out, and the skin in these regions becomes thickened and wrinkled, giving the characteristic " leonine " expression. The nodules, composed of cellular granulation-tissue, are at first reddish or slightly bluish in colour, and then very slowly become pale, firm and of varying size, and may extend so as to involve mucous surfaces. This cellular infiltration occurs especially round the blood-vessels, and is made up of numerous mononuclear cells, some of lymphocyte-type, and others with a single pale vesicular nucleus and abundant vacuolated cytoplasm. These latter are wandering phagocytic cells. They become crowded with bacilli, and have been called " lepra-cells." New blood-vessels are present, but the granulation-tissue of leprosy is not characterised by vascularity, nor does it undergo caseous necrosis. On the surface of the body, the nodules tend to break down and give rise to irregular ulcers ; and, in the neighbourhood of these, extensive fibrous cicatrisation occurs. This development of fibrous tissue may take place without ulceration. By the formation of the nodules, and by their ulceration and cicatrisation, extensive and unsightly deformities are produced. Similar nodules are found in the liver and spleen.

Lepra Anæsthetica or **Maculosa.** In this form, the principal lesion is in the peripheral nerves (p. 1187), on which are seen spindle-shaped swellings, composed of granulation-tissue formed from the perineurium. This granulation-tissue is rich in bacilli and " lepra-cells " ; and, partly by pressure, but mainly by infiltration, its growth causes degenerative changes in the nerves themselves. These granulomatous formations are seen occasionally in the brain or spinal cord. The nerve-affections give rise to neuralgias, and also to trophic disturbances leading to atrophy in the skin, the bones, and other tissues. In the skin, localised patches of anæsthesia occur ; and, in these, there may be a diminution or an increase of pigment, leading to the production of whitish or brownish areas respectively, which are liable to ulcerative or other necrotic changes. The destructive effects, aided, no doubt, by the results of infection with pyogenic organisms, may be extensive and lead to the production of periostitis, osteomyelitis, caries and necrosis especially of the phalanges, with atrophy of the bones and, not uncommonly, falling off of the fingers or toes. The nose, hands, feet, and even large parts of limbs may separate and drop off as a result of these necrotic processes.

Very commonly, the two forms of leprosy are co-existent. Nodular masses of leprous tissue, containing enormous numbers of the specific bacilli, may occur in the lymph-nodes, liver, spleen, testes, lungs or kidneys. The kidneys are sometimes seriously affected and in many instances show advanced atrophic changes. But, besides the larger foci of infection, microscopic lesions are not infrequent. The bacilli can be easily demonstrated in the internal organs and are found in enormous numbers in some of the discharges, *e.g.*, from the ulcerating nasal mucous membrane.

SYPHILIS[1]

This disease, which is so common in man, does not occur naturally in the domestic or wild animals, but can be transmitted experimentally to the anthropoid apes and some of the lower monkeys, and to the rabbit by inoculation of infected material into the testis, the cornea or the anterior chamber of the eye. The causal organism, *Treponema pallidum* (*syn. Spirochæta pallida*, p. 372), is a long, slender, actively motile, spiral, thread-like body, the curves, six to fourteen in number, being regular, narrow, and deep. The organism is invariably present in the initial lesions and in the exudate from such lesions, and can be demonstrated by use of dark-ground illumination and by other methods. It can be found also in the mucous patches and condylomata, in the papules, in the enlarged lymph-nodes, in the blood from the roseolar rash, and, less frequently, in the circulating blood in the secondary stage of the disease. It occurs in the blood and in the organs and tissues of infants suffering from congenital syphilis; and it has also been demonstrated in the tertiary lesions of the disease, *e.g.*, at the margins of gummata and in syphilitic patches in blood-vessels : and in the brain in general paresis (Fig. 611, p. 1013).

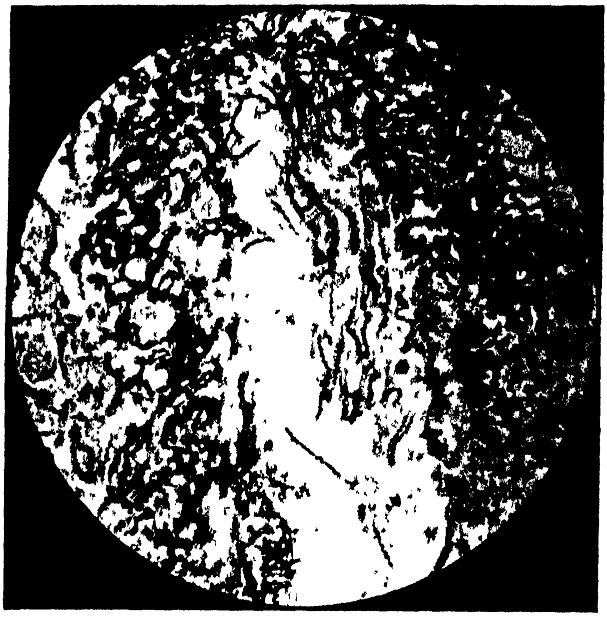

FIG. 45. Spleen from a case of congenital syphilis, showing numerous spirochætes. Levaditi's silver-impregnation method. × 1000.

Method of Infection and Spread. Syphilis is usually transmitted by sexual intercourse with an infected individual, but the use of infected drinking-vessels, dental instruments and even of bath-water is sometimes the means of conveying the organism to man. The spread within the body is mainly by the lymphatics, and the lymph-nodes in the neighbourhood of the primary lesion soon become involved. The presence of the organism in the circulating blood proves that it must be spread also by this means. There may be direct passage of the organism through the placenta from the mother to the fœtus.

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[1] The word "Syphilis" was used by Girolamo Fracastoro (1483–1553), a learned Italian physician and poet, who wrote a book called "*Liber Syphiludis seu Morbi Gallici*" (Verona, 1530), the title being derived from the name of a swine-herd, "Syphilis," a character in one of his poems. The name itself was derived from *σῦς*, *sus*, or *ὗς*, *hus*, a swine (*cf.* *συφεός*, *supheos* or *sypheos*, a pig-sty) and *φιλεῖν*, *philein*, to love.

Morbid Anatomy and Histology. The course of the disease may be divided, more or less arbitrarily, into three stages :—

(*a*) **Primary Lesion or Chancre.** This occurs most commonly about the external genitals, but may be found on other parts of the body which have been in contact with the syphilitic lesion, *e.g.*, lips or nipple, and also the fingers of doctors or nurses. After a period of incubation of about three weeks or more, a papule or a vesicle, which is usually red and inflamed, makes its appearance; the base becomes indurated, and is " cartilaginous " to the touch. This **hard, indurated** or **" Hunterian " chancre** becomes superficially ulcerated. Microscopically, it is of chronic inflammatory nature, and is composed at first of rounded lymphoid cells, which soon become mingled with proliferated connective-tissue cells—rounded and spindle-shaped—and plasma-cells. Giant-cells are rarely present. The blood-vessels show thickening, especially of their inner coat. The newly-formed tissue tends to remain undeveloped—*i.e.*, the cells do not proceed to the formation of fibrous tissue—and cicatrisation is therefore not a usual sequel unless secondary infection with pyogenic organisms has also occurred, in which case the granulation-tissue develops into fibrous tissue and a scar may be produced. During the process of healing, the chancre gradually disappears and leaves little evidence of its previous presence. The organisms travel by the lymphatics to the neighbouring lymph-nodes, which become enlarged and hard, and, on the microscopical examination of biopsy puncture-fluid, show the presence of the spirochæte. Histologically, masses of irregularly-formed granulation-tissue, similar to that of the chancre, are found.

(*b*) **Secondary Lesions.** These are usually generalised and more or less symmetrically distributed. Thus, both arms, and both sides of the chest show the secondary **rash.** This suggests a distribution of the causal agent by means of the blood-stream, in which the spirochætes are present within a few hours after infection. The lesions become evident in from three to four weeks up to several months after the primary infection and are accompanied by fever and other constitutional symptoms. They are usually in the skin, where they show as a roseolar rash or as a papular, macular or scaly eruption which generally causes little or no irritation. Periostitis and pharyngitis may also occur; and slightly raised nodules showing superficial ulceration—the mucous patches and condylomata—are seen on mucous membranes and in the neighbouring skin, *e.g.*, of the mouth (p. 705), the pharynx, the vulva, or the anus. The microscopical appearances of the mucous patches and condylomata are similar to those of the primary chancre, and the spirochætes are found in large numbers in these lesions and also in the lymph-nodes, which often show widespread enlargement, characterised by proliferation of the endothelial cells of the sinuses and thickening of the reticulum.

(*c*) **Tertiary Lesions.** These are characterised by the presence of local tumour-like formations or **gummata**; but there are always also associated more or less diffuse syphilitic changes in the arteries, and in various internal organs, *e.g.*, the liver and lung. Gummata are whitish or greyish in appearance, commonly with a yellow caseous centre. They vary considerably in size, from microscopic nodules to those the size of a large orange. They are not definitely encapsuled; but the periphery generally merges into a firm connective tissue, which extends into the surrounding structures, and is a new formation. Microscopically (Fig. 604, p. 1005), a gumma is composed of masses of lymphoid and proliferated connective-tissue cells, which may be rounded, irregular, or spindle-shaped in outline. Giant-cells and endothelioid cells may also be present. The giant-cells resemble those seen in tuberculosis, but are smaller and more irregular, and show less definite caseation in their centres. The blood-vessels show thickening of their intima, and periarteritis is common. Gummata may be found in almost any of the tissues or organs of the body, but most frequently in the periosteum and bone, though they are also common in liver and brain (pp. 86–7 and 1005). If the gummata are situated in mucous membranes, *e.g.*, about the mouth, tongue, soft palate, pharynx or tonsils, or in tissues close to the skin-surface, the necrotic changes may lead to ulceration and widespread destruction in these tissues, and to erosion of cartilage or bone, with perforation of the palate. Later, such gummatous lesions tend to shrink, and the associated chronic inflammation leads to cicatricial contraction, scarring and often deep depressions. Apart from gummata, **diffuse fibrous infiltration** is characteristic of syphilis. The infiltrations are mainly of the nature of fibrous overgrowths, composed at first of cellular and vascular granulation-tissue, and later of well-formed fibrous tissue. These infiltrations are seen in the liver and lungs, and in both the inner coat and adventitia of the arteries. Strictures of the cardiac and

FIG. 46. Syphilitic disease: Vertical section of spleen. Malpighian bodies enlarged and translucent from amyloid infiltration. Immediately beneath the convex surface were three opaque, pale-yellow, firm, caseous gummata, the largest about three-quarters of an inch in diameter. (From a woman with congenital syphilis, who died aged 27 years.)

pyloric orifices of the stomach and of the intestine, especially at the anus, may be produced. Amyloid degeneration occurs in the vessels and connective tissue of various organs (p. 210 *et passim*) in old-standing, untreated cases.

Syphilitic disease produces numerous and important lesions in the nervous system (p. 1002 *et seq.*), including those seen in general paresis of the insane and tabes dorsalis, which are described on pp. 1010–11 and 1016.

CONGENITAL SYPHILIS. Syphilis may be developed *in utero*, and the fœtus may die in the uterine cavity and be aborted, either in a macerated condition or well-formed and apparently healthy ; or the child may be born with syphilitic lesions. The disease may, on the other hand, be acquired during birth, by contact with syphilitic lesions in the passages of the mother. The former alone is, in the strict sense, congenital syphilis, and, in the aborted fœtus, the spirochætes are found, usually in enormous numbers, in the liver, spleen, etc. In the congenital form, the changes are practically the same as those of acquired syphilis, but modified by the fact that they are produced in young, growing tissues. Thus, affections of the skin, in the form of a roseolar rash and papular eruptions, fissures and maculæ, inflammations of the cornea and sclerotic and inflammation of the mucous membranes occur. In addition, the wedge-shaped or peg-like teeth and the notching of the upper central incisors (Hutchinson's teeth) are commonly seen. In true congenital syphilis, the inflammatory changes are present, but the more characteristic lesions are of a chronic nature. They are seen in the liver, lung, periosteum, dura, pia-arachnoid and brain (p. 1020), in the bones, and in the arteries ; and are mainly of the nature of a diffuse overgrowth of fibrous tissue, which, by its invasion of functioning tissues and later by its contraction, leads to atrophy and absorption and the production of irregular scars and fissures. Gummata are sometimes present.

SYPHILITIC LESIONS IN VARIOUS ORGANS AND TISSUES

1. **Brain, Spinal Cord and Membranes.** The changes in these organs and tissues are dealt with under Diseases of the Central Nervous System (pp. 1002 to 1021), but it should always be remembered that the involvement of the nervous system occurs also in untreated or in inadequately treated cases, and that, with inadequate treatment, the period between infection and the onset may vary considerably in individual cases. In such cases of persistent or so-called "latent" syphilis, spirochætes which have resisted treatment may survive in some of the more inaccessible parts of the nervous and vascular systems ; and evidence has recently been brought forward to suggest that they may also survive especially in certain of the lymph-nodes, *e.g.*, in the mediastinum and abdomen, and thence subsequently re-infect the spinal ganglia, thus producing tabes dorsalis (p. 1016) : or in the walls of the larger blood-vessels, especially the aorta, leading to the production of chronic cardiovascular syphilis. The leptomeninges may be affected by direct extension from syphilis of the dura, the lesion presenting itself as a diffuse meningitis or as an arteritis—a peri-, mes- and end-arteritis (p. 1003).

2. **Bones and Joints.** (*a*) **Bones.** In **congenital syphilis,** the condition known as **Craniotabes,** which is sometimes associated with rickets (p. 1218), is found. In it the bones of the skull become thinned and softened at parts. Areas

in the cranial bones, especially those of the occipital region, may be thin, atrophied and capable of being indented with the finger on slight pressure. In the long bones, the cartilage-cells in the ossifying areas may undergo proliferation, and be associated with irregular calcification of the matrix; and, adjacent to this ossifying area, there is sometimes an excessive formation of *granulation-tissue or even of soft, fluid or semi-fluid pus-like material, with separation of the epiphysis as a result. Actual lengthening of the bones sometimes takes place. A syphilitic* ***epiphysitis*** *occurs in early infancy, especially* in the growing bones which form the knee-joint and in the head of the humerus, but other epiphyses may be involved and several are often affected simultaneously. A syphilitic osteomyelitis of the phalanges, **syphilitic dactylitis,** especially of the hands but occasionally of the feet, is not uncommon in children congenitally infected.

Acquired syphilitic disease of a mucous membrane may spread to adjacent bones and cartilages, and cause erosion and perforation. Subperiosteal formation of new bone, gummata, filling-up of Haversian canals and endarteritis obliterans are associated conditions. These lesions are seen especially in the bones of the palate and of the nose.

In the long bones, subperiosteal infiltration leads to caries; and gummata, which are found in the cancellous tissue, either in the epiphysis or at the end of the diaphysis, sometimes remain latent for a long time or lead to syphilitic osteomyelitis, with erosion of the compact layers of bone and to "spontaneous" fracture.

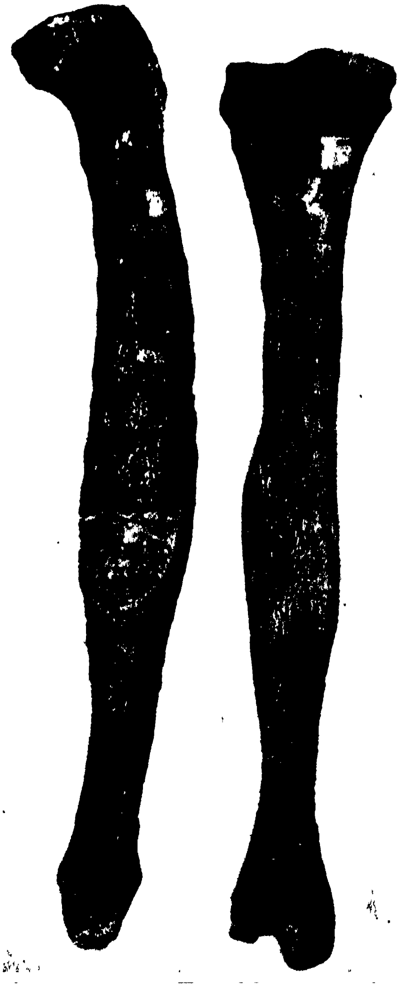

FIG. 47. Tibiæ exhibiting syphilitic nodes on their shafts.

Bone-lesions in late secondary and tertiary syphilis usually take the form of a periostitis. During the more acute stage, there is considerable local proliferation of the cells of the periosteum, and the formation of irregular periosteal nodes. Associated with these nodes, there are always chronic inflammatory changes—the medullary canal becomes narrowed or even filled up, and subperiosteal thickening of the bone is a common feature. Thus, the bones become denser and heavier than normal. Localised gummata or areas of gummatous infiltration appear under the periosteum or in the cancellous tissue. As a gumma increases in size, its central part becomes caseous, and the bone underneath shows an irregular eroded surface. In some instances, *e.g.*, in the bones of the skull, this erosion is extreme, and necrosis, with the formation of sequestra, and a "worm-eaten" appearance of the surviving bone, is produced, and perforation perhaps supervenes (Fig. 602, p. 1004). The sequestra, in some cases, remain for years only partially separated. The gummata sometimes undergo softening and become infected with pyogenic organisms, with the formation of an abscess. If healing takes place, the subperiosteal thickening and perforation usually persist.

The bones specially affected by syphilis are the tibia, the ulna, the parietal, occipital, and frontal bones, the clavicle, the sternum, and the ribs.

(*b*) **Joints.** In **congenital** syphilis, arthritis may occur, with exudation into the joint-cavity, which comes on very rapidly, and which is often bilaterally symmetrical. The capsule of the joint becomes thickened, and ulceration of the cartilages occurs. In **acquired** syphilis, gummatous infiltration of the tissues round the joint sometimes extends into the cavity and involves the synovial membrane, with the production of a chronic arthritis. More rarely, the arthritis is caused by the invasion of the joint-cavity by a gumma arising in a neighbouring bone. Erosion of the cartilage is sometimes present. "Charcot's" and other forms of affection of the joints—"arthropathies"—seen in tabes dorsalis (locomotor ataxia), are described on p. 1239 and Fig. 797, p. 1240.

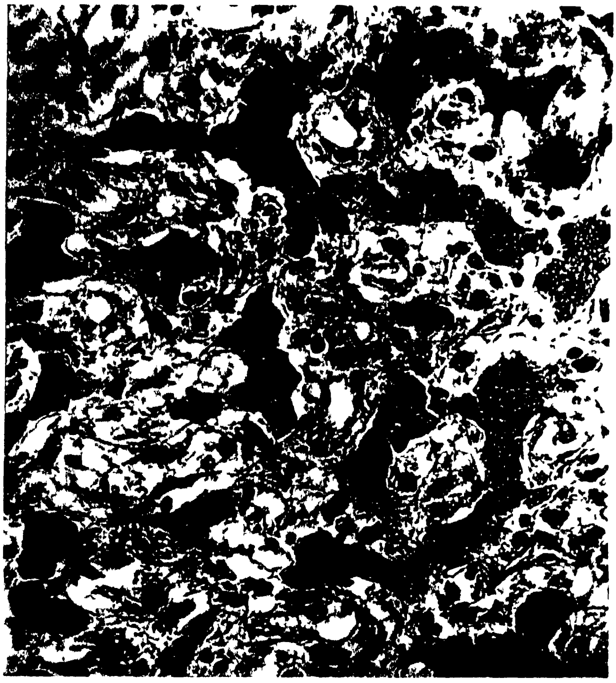

FIG. 48. Liver. From a case of congenital syphilis, showing diffuse overgrowth of connective tissue (intercellular cirrhosis). × 300.

3. **Liver.** The changes in the liver may be pronounced, and vary, in some degree, according to whether the disease is congenital or acquired.

Congenital syphilis in infants manifests itself specially in the liver, which is usually enlarged, and smooth on the surface. On naked-eye examination of the cut surface, gummata, mostly of small size, may be seen, and rounded translucent areas which are connected with the hepatic artery are often present. On microscopical examination, diffuse interstitial hepatitis is seen, the connective tissue being highly cellular, and appearing to develop first between the liver-cells and the endothelium of the capillaries. The lobular outlines become indistinct, and the radiate arrangement lost—the cells being separated into small isolated clumps by the diffuse spread of the fibrous tissue—the **intercellular,** unicellular (or so-called " monocellular ") **cirrhosis** of Charcot. Cellular foci, some with caseous centres and others without evidence of degenerative changes, are seen scattered throughout sections of the liver. The latter are the " translucent areas " referred to above and are associated with branches of the hepatic artery showing periarteritis and endarteritis. Probably both of these types of cellular reaction should be classed as gummata. In children, fibrous cicatrices—surrounding and isolating islets or " lobed " rounded masses of liver-tissue—may be present a few months after birth. In and around the miliary gummata, in the young granulation-tissue round the vessels, in the walls of the vessels, and in and around the liver-cells, spirochætes, sometimes in enormous numbers, can be demonstrated by special methods. Amyloid degeneration and perihepatitis may also be demonstrable.

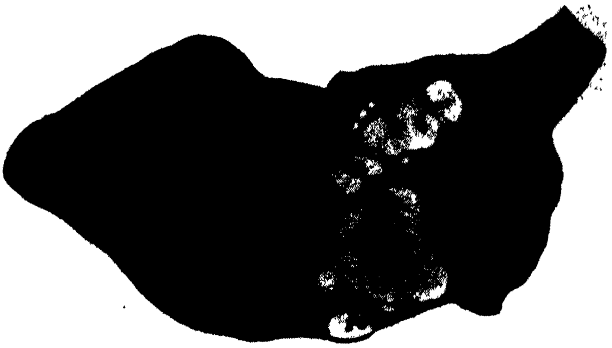

FIG. 49. Multiple gummata in the liver. (Dr. Norah Schuster's case.)

In **acquired syphilis,** the changes are usually more localised than in the congenital form, and are evident especially towards the superficial parts of the liver. The usual evidence of this form of syphilis is the presence of cicatrices, sometimes numerous, especially near the suspensory ligament. At the bottom of these cicatrices, gummata, varying in size, and fibrous bands spreading into the neighbouring liver-tissue, are seen, though, in long-standing cases, they may become entirely absorbed and replaced by fibrous tissue. Similar scars are seen occasionally in the spleen. The gummata almost always show a caseous centre, surrounded by a zone of fibrous tissue. Perihepatitis is sometimes extensive, frequently giving rise to firm fibrous adhesions between the liver and the diaphragm, etc.; and the capsule may show irregular thickening. Amyloid disease, regular or irregular in distribution, is sometimes present (Fig. 103, p. 211). On account of anti-syphilitic treatment in the early stages of the disease, the presence of amyloid degeneration and the development of gummata are now seldom seen by clinicians or pathologists.

4. **Nose, Larynx and Trachea.** In the **nose,** mucous patches occur in the secondary stages of the disease and a catarrh (" snuffles ") is present in congenital cases. Catarrh of the **larynx** and **trachea** is associated with any of the stages of the acquired disease. The more characteristic change in all these tissues is an irregular infiltration with granulation-tissue, gummatous in nature and causing deep, irregular ulceration. The ulcers cause considerable destruction, not only of the mucous and submucous tissues, but also of the cartilages; and perforation may result. The newly-formed infiltrating tissue undergoes cicatrisation; and irregular contraction and partial stenosis are produced. In the larynx, syphilitic ulcers are found most commonly at the upper part in the region of the vocal cords, but they occur at other parts, and bring about secondary involvement of the trachea and larger bronchi, especially near the main bifurcation. They give rise to perichondritis, more particularly of the cricoid cartilage. In the nose, perforation of the septum and of the palate, and destruction of the nasal bones with depression of the bridge, occurs.

5. **Lungs.** In **congenital syphilis,** gummata are found, but the most characteristic change is an **interstitial pneumonia.** The lung is usually pale in colour and tough, and is intersected by delicate fibrous bands. This change, "white hepatisation," or "white pneumonia" as it is sometimes called, is widely spread, or confined to a small portion of the lung. Microscopically, the connective-tissue overgrowth is, at first, highly cellular and vascular, but, later, it may become more densely fibrous. The alveoli undergo compression, their walls are invaded by fibrous tissue, and the lining-cells become cubical or spheroidal. As the overgrowth continues, the air-vesicles become more and more collapsed, and secondary changes such as atrophy and obliteration result. Large numbers of spirochætes may be present.

In **acquired syphilis, gummata** are found, and are often surrounded by well-formed fibrous tissue. This tissue may contract and the gummata be absorbed, leading to the production of irregular cicatrices, most frequently in the posterior and outer parts of the lower lobes. **Interstitial overgrowth,** similar to that seen in congenital cases, may occur. The fibrous tissue is, however, much less cellular. The fibrous bands which intersect the lung-tissue are situated usually at the posterior or outer aspect of the lower lobes, where they pass from the pleura inwards, and may be traced to, and be continuous with, the sheaths of some of the larger bronchi. By their contraction, irregular and deep puckered cicatrices are produced on the surface In or in relation to these fibrous bands, gummata or their remains may be found. In some cases of syphilitic ulceration or stenosis of the larynx, the retained secretion gives rise to retention-pneumonia and to bronchiectasis, and diffuse syphilitic interstitial pneumonia. Not uncommonly, secondary infection with tubercle bacilli and other organisms occurs.

6. **Heart.** Gummata sometimes occur in the heart-muscle, and usually are associated with considerable fibrosis. If invasion of the conducting fibres or of the primitive muscle-tissue of the heart takes place, heart-block (p. 474)

follows. An interstitial myocarditis is caused by syphilitic endarteritis of the coronary arteries. In congenital syphilis, the characteristic lesion is an interstitial infiltration of "myxomatous" connective tissue rich in mononuclear cells. This young connective tissue may appear as subepicardial and myocardial nodules which are called "myxogummata." These lesions are extremely rich in spirochætes.

7. **Arteries.** The arterial changes due to syphilis are described in the section on Disease of Arteries (p. 479 *et seq.*).

8. **Stomach.** Gummatous infiltration and ulceration, sometimes multiple, and usually at the greater curvature, may simulate malignant disease and produce gross deformation of the organ.[1]

9. **Intestine.** Occasionally during the tertiary stage of syphilis, gummata are formed in the large intestine, especially the rectum. The condition spreads transversely round the bowel, and leads to stenosis. Sores at the anus and inflammatory areas in the ileum have been described in the primary stage of the disease. It is now established, however, that many of the examples of rectal stenosis, which would previously have been attributed to syphilis, are due to lymphogranuloma inguinale (pp. 104 and 755), which may also occasionally attack the stomach.

10. **Endocrine Glands.** In the thyroid and suprarenal glands, gummata and interstitial fibrosis as a result of syphilis are rare.

11. **Genito-urinary System.** Apart from the primary sore, which is described on p. 81, a frequent lesion in the genitals is gumma in the testis. This starts in the body of the organ and causes considerable enlargement with necrosis. The testis shows patchy fibrosis as a sequel of interstitial orchitis. In the kidney, interstitial fibrous overgrowth, leading to some form of interstitial nephritis, takes place, due in part to the syphilitic endarteritis of the renal vessels. Amyloid degeneration of the kidney and other organs, due to syphilis, is described on p. 210 *et passim.*

Lymphogranuloma Inguinale or Climatic Bubo. This disease is described under viral infections on p. 104, and *see also* p. 755.

FRAMBŒSIA or YAWS. This is a granulomatous disease which occurs in certain tropical countries such as the West Coast of Africa, the West Indies, Ceylon and elsewhere, and is characterised especially by cutaneous lesions. It is caused by the *Treponema pertenue* or *Spirochæta pertenuis* (p. 373). The primary lesion is a vesicle or pustule which occurs on a skin-surface such as that of the hand. The secondary lesion which results from contact with a primary sore presents itself as a series of flattened vesicles, which later become pustular. There is thickening of the epithelium and dense infiltration of the subepithelial tissues with plasma-cells. The Wassermann reaction is usually positive. Though some writers consider this disease to be a non-venereal form of syphilis affecting races living under poor hygienic conditions, the commonly accepted view is that it is not "venereal" and is distinct from, but closely allied to, syphilis.

BEJEL. According to Hudson (1936 and 1937–38) this disease, "the epidemic syphilis of the Euphrates Arabs," is highly contagious and is usually contracted by and from children, non-venereally. In a series of 757 adult cases recorded by him, 60 per cent. had contracted the disease in childhood and only 6 per cent. after the age of thirty. The disease has little effect on the general constitution and exhibits in the early stage greyish, non-ulcerative patches on the oral mucous membrane. The saliva and scrapings from the patches contain large numbers of spirochætes of the morphology and motility characteristic of *Treponema pallidum.* There may be tenderness and swelling of the epiphyses and periosteum of the long bones, and the infection may spread from the oral patches to the mucous membrane and bones of the nose, sometimes producing softening and collapse of the nasal bridge. A papular rash may be present on the trunk and extremities, and especially in the folds in the skin. In the course of a year the early lesions disappear. After a "latent" period, which may last several years, late lesions appear in most individuals. Ulceration may occur in the soft palate, tonsils and pharynx, with extension to the larynx or the bones of the nose and hard palate—these bones becoming invaded and destroyed. By ulceration of the lesions in the skin (" gummata "), fungating masses of granulation-tissue are produced which become covered with a thick crust or scab. Periostitis of the long bones and especially over the tibial crests occurs—the site often being determined by trauma. The blood-reaction is positive to both the Wassermann and the Kahn tests and it is stated that 75 per cent. of adult Bedouins give positive serological reactions. There is little clinical evidence of involvement of the nervous system, though the reactions in the cerebrospinal fluid are occasionally positive. Hudson states that the damage done by the spirochæte in the nervous system does not apparently extend to the point where clinical symptoms of neurosyphilis are produced. C. M. Hasselmann[1] visited the country lying between the Mediterranean and the Persian Gulf and investigated diseases known locally as " Bejel," and by the other names noted below in the title of his paper. He came to the conclusion that most of these are syphilitic in nature ; though a few of the cases may have been due to various other skin-infections. The lesions most frequently seen by him involved the pharynx and mouth in children, whilst those in the bones were commoner than in the skin. Syphilitic abortion and miscarriage were common. The belief that syphilis is spread amongst Arabs exclusively by means other than sexual intercourse Hasselmann considers to be a " myth," and he believes that the terms " venereal," " non-venereal," and " genital " and " extra-genital " are often misapplied in this connection. Speaking generally, he holds that syphilis runs the same course in the Near East as elsewhere.

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[1] J. T. Priestley and W. Walters, Mayo Clinic, *Surg., Gynecol. and Obstet.*, 1934, **58**, 1030 : Theodore Thompson and L. H. Howells (London), *Quart. Jour. Med.*, 1935, New Series, **4** 81 : A. Landau and J. Held, "La Syphilis gastrique," 1936, Masson, Paris.

GLANDERS

This is a disease attacking especially the horse and the ass, but it can be communicated to man. The causal organism is *Pfeifferella mallei*, and the disease occurs in either an acute, or a chronic, form. In the **horse,** the acute form manifests itself by the formation of granulation-tissue swellings of the mucous membrane or skin. The disease commences in the mucous membrane of the nose, and spreads to the adjacent lymph-nodes, and along the mucous membrane of the bronchi to the lung. In **man,** the disease is usually very acute and rapidly fatal. Nodules and ulcers appear in the mucous membranes or in the skin ; and a diffuse spreading inflammation, with purulent infiltration between the muscles, and abscesses in the lung and other internal organs, follows, death supervening in these cases from pyæmia. The nodules in glanders are largely inflammatory in nature, with dense aggregations of leucocytes, mostly polymorphonuclear in type, in the centre. The inflammatory change may be followed by necrosis and suppuration. If near the surface, ulcers are produced. In the more chronic forms, which are rare in man, there is a spreading inflammatory reaction along the lymphatics, with enlargement of the lymph-nodes, giving rise to irregular " cords " and " knots." To this condition the name **farcy** has been applied, and the swellings are spoken of as " farcy-buds." In these, there is an overgrowth of connective-tissue ; and necrotic changes and ulceration are liable to occur. The overgrowth of fibrous tissue is sometimes seen in the lungs and generally arises by a proliferation of the peribronchial and perivascular connective tissue.

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[1] C. M. Hasselmann, " Syphilis among Arabs in the Near East : Bejel and Loath in Iraq and Syria ; Firjal and Latta in Palestine ; Laghout in Lebanon ; Abou-Laghif and Jifai in Trans-Jordan." (*Arch. Dermat. & Syph.*, 1938, **38**, 837–855.)

TULARÆMIA. This disease is common in ground-squirrels, wild rabbits, hares and beavers and possibly in game-birds, and, in Norway, amongst lemmings. It is widespread in the United States, but it occurs also in Europe ; and in Japan it is known as " **Ohara's disease.**" The infection is conveyed to man by biting-insects, such as the horse-fly and deer-fly, by ticks, but most commonly by direct contact with the carcases of diseased animals, as in the skinning of infected rabbits—hence the popular name " deer-fly fever " or " rabbit-fever." It is probably also carried by contaminated water.[1] Infection from man to man has not yet been recorded. Test-tube cultures of the causal organism, *Bacterium tularense*, retain their virulence for long periods, and several laboratory-workers have become infected when handling them, suggesting that the bacteria are capable of passing through the unbroken skin and mucous membranes. In man, two main clinical types of the disease are recognised—the **glandular** and the **typhoidal**. Of the former, the commonest subvariety is the **ulcero-glandular,** in which a primary papular lesion, which later undergoes necrosis, ulceration and suppuration, develops in the skin, and the regional lymph-nodes become enlarged, inflamed and necrotic. Sometimes the portal of entry is the eye, and the pre-auricular, submaxillary and cervical nodes tend to become involved, constituting the **oculo-glandular** variety. In fatal cases, death usually supervenes from a tularæmic **septicæmia** or a tularæmic **pneumonia,** and from the latter condition recovery is rare. On post-mortem examination, necrotic nodules and a reticulo-endothelial hyperplasia are found in the liver and spleen. Microscopically, the primary ulcer presents a caseous base surrounded by a zone of polymorphonuclear cells and, external to this, another of endothelioid cells. In the less acute, and in chronic, cases, both the primary ulcer and the lesions in the lymph-nodes exhibit a reticulo-endothelial hyperplasia with the presence of giant-cells, and may be mistaken for tuberculosis. In the typhoidal type, no obvious primary lesion is to be found, there is no enlargement of regional lymph-nodes, and the disease closely resembles typhoid fever. Blood-culture is practically uniformly positive during the first week in both types of the disease ; and, towards the end of the second week, specific agglutinins are present. It is claimed that these agglutinins reach their maximum about the end of the third week, and then gradually decline : but that minor degrees of agglutination may persist for years. As cross-agglutination with *Brucella melitensis* occurs, the infection may in late stages be confused with undulant fever.

Rhinoscleroma. This disease, which is practically confined to Eastern Europe, is characterised by the presence of small hard nodules in the skin and mucous membranes of the nose, pharynx, larynx and upper trachea. The nodules are composed of granulation-tissue in which large round cells, filled with a gelatinous material, and the nuclei of which are pushed to one side, are present. These "Mikulicz's cells" contain groups of a short Gram-negative bacillus (*Encephalatus* or *Klebsiella rhinoscleromatis*), but the causal relationship of this organism to the disease has not been proved.

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[1] Public Health Report, Washington, February 9th, 1940, p. 227.

MYCOSES[1]

ACTINOMYCOSIS. This disease is common in oxen, so-called "woody tongue" and "lumpy jaw" being its principal manifestations. It occurs with comparative frequency also in man. In cattle, tumour-like nodules are present on various mucous or serous surfaces, or as large masses about the jaws and tongue—the last being the commonest site of the disease. These masses are composed of granulation-tissue containing the causal organism, *Actinomyces bovis* (*syn. Streptothrix actinomyces*)—the "**ray-fungus.**" The nodules tend to become fibrous or calcified, though extensive suppuration occurs in some of them. The lesions in the human subject are usually of a suppurative character, and the primary focus is about the mouth or pharynx, the intestinal tract, especially the cæcum and appendix, and in the lung. In the mouth, the organisms gain entrance around a decayed tooth or through some abrasion of the mucous membrane, and in this situation an irregular mass of granulation-

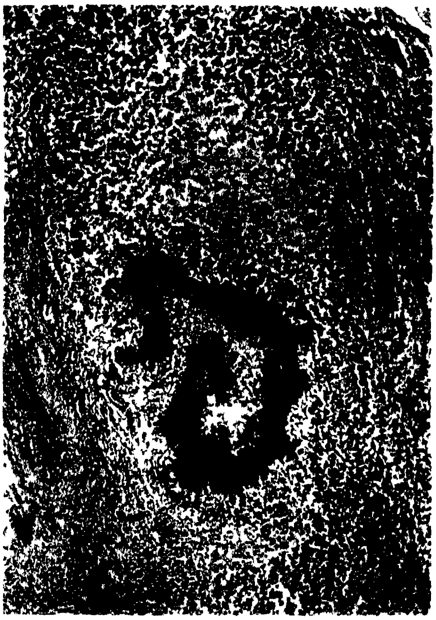

FIG. 50. Actinomycotic abscess in the lung of a man aged about 40 years, showing a darkly-stained mass of *Actinomyces bovis*. Gram's method. × 60.

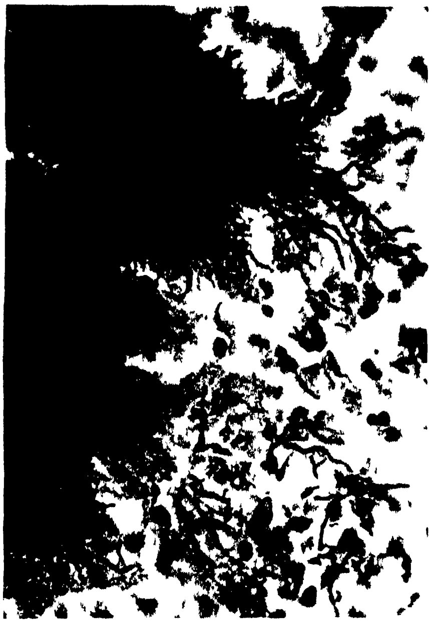

FIG. 51. Margin of mass of *Actinomyces bovis*, showing branching filamentous structure. Gram's method. × 500.

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[1] Greek μύκης, *mukēs* or *mykēs*, a mushroom, and hence a fungus, so called because of its moist "mucous" or "mucoid" character.

tissue, with scattered foci of suppuration, is produced. The disease spreads through the surrounding tissues in all directions, forming winding, suppurating sinuses which open on the skin-surface and lead from areas of necrosed bone, fibrous and granulation-tissue. In the lung, infected probably by way of a bronchus, and in the intestine, the lesion is characterised by chronic suppuration. Metastatic abscesses may occur in any of the internal organs. The liver is the commonest site, but the lungs (p. 568A), brain, kidneys, and the breast may contain such abscesses.

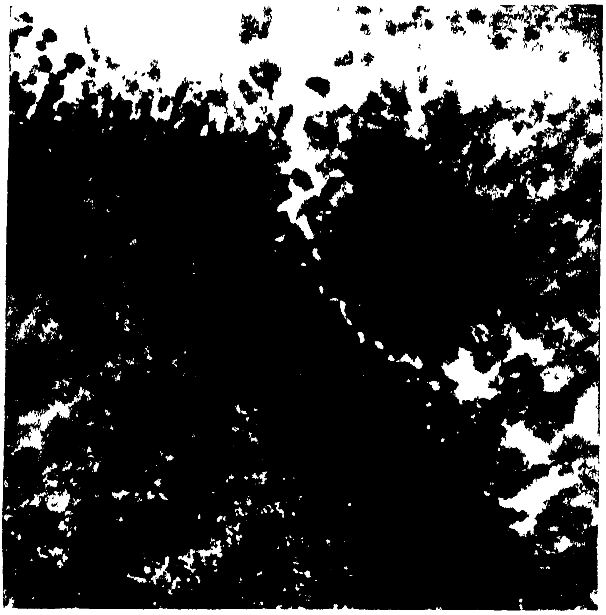

FIG. 52. Margin of mass in human lung, showing " clubbing " of extremities of the filaments of *Actinomyces bovis*. Gram's method. × 500.

The pus is thick, yellowish or greenish in colour, and contains small yellowish-grey or black masses, which are soft, and, on microscopical examination, prove to be masses of the organism in the form of branching filaments.

Closely allied to actinomycosis, and producing, in man, similar suppurative lesions, with necrosis and sometimes pyæmia, several conditions have been described in which the causal organism resembles, in many respects, the *Actinomyces bovis*. Of these, the most important are **Mycetoma,** or **Madura-foot,** due to *Actinomyces maduræ* (*syn. Streptothrix maduræ*) : and the pyæmic conditions produced by *Actinomyces asteroides* (*syn. Streptothrix asteroides*) of Eppinger. This latter organism may produce minute abscesses in enormous numbers in the lung—the condition simulating an acute miliary tuberculosis (pp. 550 and 568A).

A considerable group of **Hyphomycetes** or " **Fungi Imperfecti** " and " **Yeast-like Organisms** " still await definite classification. Amongst these may be included the so-called *Cryptococci*, *Monilias*, *Parasaccharomyces*, *Torulæ* or Yeasts, *Blastomyces*, *Coccidioides*, *Pityrosporum*, *Endomyces*, *Mycoderma*, *Oïdium*, and other still doubtful and indefinite Genera. Some of these " Fungi Imperfecti ", (amongst which many of the organisms to which reference is made in the following paragraphs must still be placed), develop especially in the horny layers of the skin or in and around the hairs or nails, producing varying degrees of irritation, inflammatory reactions and, not infrequently, purulent exudates. Amongst the more important of these are the parasites of **ringworm** and **favus.**

Blastomycosis.[1] Organisms belonging to the **Blastomycetes Group (Cryptococcus** and **Monilia)** have been isolated from the tissues in many conditions in which there is sometimes insufficient evidence that they are causal; but, in certain forms of dermatitis associated with suppuration, such as paronychia, the organisms undoubtedly multiply and produce pathological lesions. In the earlier described cases, attention was directed especially to nodules and abscesses in the lung, but the primary lesion is cutaneous (p. 568A) and there may be no involvement of the lung. This type, described by Gilchrist and known as "**Gilchrist's disease,**" is found especially in the northern part of the Mississippi Valley and in the Middle West. It is due to *Blastomyces dermatitidis* (*Gilchristia dermatitidis* or *Cryptococcus gilchristi*), a doubly-contoured yeast which reproduces by budding and does not have filaments. The resulting cutaneous granuloma is both verrucous and ulcerative, and at the edge of the ulcer there is a marked proliferation of the epidermis, even simulating an epithelioma. In the papillary layer of the corium, at the site of the lesion, multiple miliary abscesses develop, and in these the organisms can frequently be found. The entire lesion is rich in polymorphonuclear leucocytes, lymphocytes and plasma-cells; and giant-cells, often with included parasites, are usually present. Self-dissemination to other cutaneous foci by contact may occur, but extension by the blood-stream is commoner, with resulting widespread visceral involvement, especially in the lungs.

Moniliasis. Three types of *Monilia* are recognised: **Type I** (*M. parapsilosis*) probably usually non-pathogenic: **Type II** (*M. albicans*) pathogenic in man and (experimentally) in rabbits and mice, but apparently not in guineapigs: and **Type III** (*M. candida*) much less actively pathogenic than Type II.

Monilia albicans is the common parasite of **thrush** (p. 704), and it may attack, not only the mucous membrane of the mouth and throat, but of the vagina, and also the skin, in which it causes an interdigital dermatitis: one form of onychia (the parasites of ringworm produce another form): and, especially in diabetics, an eczema intertrigo in the region of the genitals and thighs. Monilias are common saprophytes in Nature in dead and decaying vegetable matter and in animal excrement; and ***M. albicans*** is not uncommon **in the mouth and throat**; and, especially in young children and in weakly adults, it frequently becomes pathogenic (p. 704). It can also attack the **bronchi** and **lungs,** and, either as a secondary invader (*e.g.*, in tuberculosis) or independently, give rise to "**bronchomoniliasis**" and other pulmonary infections of varying degrees of severity (p. 568). It is often found in the fæces.

Coccidioidal Granuloma or "**California disease**" is due to *Coccidioides immitis*, a non-budding, doubly-contoured spherical organism which reproduces *in vivo* by endosporulation. In suitable culture-media it forms an abundant mycelium. Geographically, it is prevalent in the San Joaquin Valley in California, but occurs also in other parts of the United States. Both cutaneous and visceral lesions may be encountered. While earlier lesions are rich in polymorphonuclears, the more chronic processes become granulomatous and may resemble gummata. Diagnosis from microscopical sections requires recognition of the causal organism, as the granulation-tissue itself is not pathognomonic, and clinically the disease may simulate the appearances of tuberculosis, syphilis or blastomycosis.

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[1] Greek, *βλαστός*, *blastos*, a shoot or sprout, from *βλαστάνω*, *blastanō*, to bud, sprout or grow

Torulosis in man is due to the spherical or ovoid, budding organism, *Torula histolytica,* which is not doubly-contoured but frequently shows a mucinoid envelope about it. It produces a rapidly fatal cerebrospinal meningitis (p. 980 *et passim*) and involves also the substance of both brain and cord (p. 1053). The lytic character of the process is seen best in the cerebral cortex where the organisms in large numbers are found in cavities produced by liquefaction-necrosis of the brain-substance. Unless this possibility is kept in mind, the free organisms in the spinal fluid may, in stained preparations, be mistaken for lymphocytes. In the more rare involvement of the skin, lymph-nodes, spleen and liver, the lytic changes are seldom evident. In some instances, these tissues have shown instead a chronic granulomatous induration having some resemblance histologically to Hodgkin's disease. When the disease is primarily cutaneous, it may still produce meningitis by blood-borne dissemination.

Sporotrichosis is a cutaneous granuloma due to *Sporotrichon beurmanni* and several related organisms. The local lesion, frequently on the hand, is an indolent ulcer with an indurated, vascular, purulent, granulation-tissue base. An ascending lymphangitis with a series of new lesions is characteristic of the infection. This disease has not infrequently been contracted by injuries from the thorns of the ornamental barberry. Histologically, lymphocytes, plasma-cells and endothelioid cells occur at the periphery of the lesion, whilst the centre remains purulent. It is only with the greatest difficulty that the organism can be demonstrated in sections. Diagnosis can be confirmed by cultural methods and an agglutination-test can also be employed.

Other Pathogenic Fungi. The **phycomycetes,** which are characterised by a mycelium of non-septate hyphæ, with asexual spores contained in a sporangium or spore-case and " zygospores " formed by the conjugation of two hyphæ at their tips : the **ascomycetes,** in which the mycelium is septate and the spore-case or " ascus " is formed at the end of the hyphæ : and the " **fungi imperfecti,**" in which the life-cycle is incompletely known, are present in certain pathological lesions. In some of these, *e.g.*, inflammatory and perhaps suppurative conditions in the ear, nose and mouth, **mucors** (moulds) and **aspergilli** are found, but are often regarded as deposits and growths in, rather than as parasites causative of, the lesion. In the case of others, however, *e.g. Aspergillus fumigatus* and *Rhinosporidium seeberi,* described opposite (p. 95), the causal relationship is established.

Aspergillosis. Pulmonary aspergillosis is a form of bronchopneumonia in birds, especially pigeons, and the fungus (*Aspergillus fumigatus*) of this infection may attack the lungs of man (especially bird-fanciers), producing small grey nodules composed of necrotic tissue and associated with patches of bronchopneumonia. The nodules break down and form cavities, and in these numerous leucocytes and masses of fructifying mycelium are present. The mycelium has been found in the sputum during life (pp. 94, 503 and 568A).

Chronic pustular conditions of the external auditory meatus are sometimes associated with the presence of this and other strains of Aspergilli.

Rhinosporidiosis. This disease is caused by a vegetable parasite belonging to the phycomycetes, *Rhinosporidium seeberi* (pp. 382 and 503), and occurs almost exclusively in males, especially natives of India. The first case, reported by Seeber (1900), was in an Italian who from infancy had lived in South America; but examples of the infection reported by Minchin and Fantham (1905–6), Beattie (1906–7), and later cases, were all in Indians. Ashworth[1] (1923) worked out the life-history of the parasite, and his account, based on careful examination of the disease in an Indian student, has become classical and his conclusions have been accepted by all subsequent writers. The characteristic lesion is in the form of an inflamed polypus in the nose—the inflamed tissue being crowded with small parasitic cysts, possessing a chitinous envelope in which there is a thin area or germinal pore (Fig. 53). Within the cyst-wall, in the case of the mature parasite, there are large numbers of spores, the sporangium enlarges, and the spores escape through the germinal pore and are carried by the lymphatics into the surrounding connective tissue, where a new generation is developed. The mode of transmission and infection is unknown. As noted, the commonest site of the lesion is in the nose, but infections of the ear and of the conjunctiva have been reported.

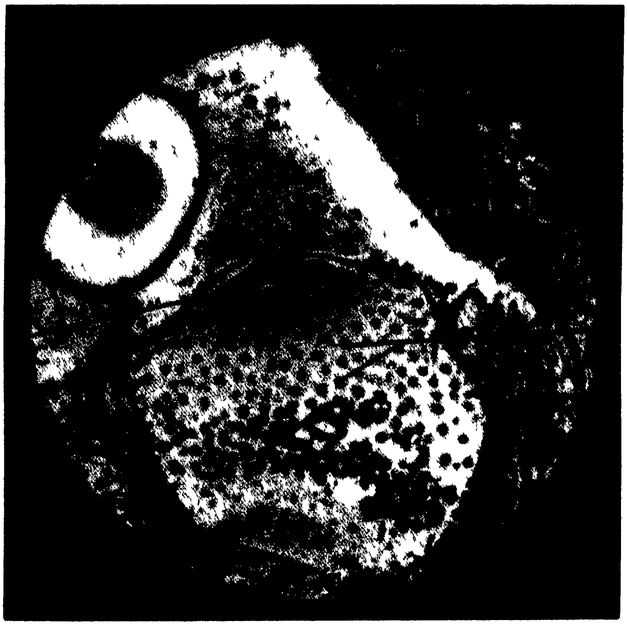

FIG. 53. Rhinosporidiosis. High-power view of a ruptured and discharging sporangium (*a*) Immature spores: (*b*) Fully developed spores: (*c*) Residual cytoplasm. Iron-alum hæmatoxylin and light-green. × 300.

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[1] "On *Rhinosporidium seeberi* (Wernicke, 1903), with Special Reference to its Sporulation and Affinities," by J. H. Ashworth, *Transactions of the Royal Society of Edinburgh*, 1923, **53**, 301–342: and "*Rhinosporidium kinealyi*," by J. M. Beattie, *Jour. Path. and Bact.*, 1906, **11**, 270.

CHAPTER IV

VIRAL INFECTIONS[1]

For a number of diseases obviously of an infective nature occurring in man, the lower animals and plants,[2] no specific causal organism easily visible under the ordinary powers of the microscope has been satisfactorily demonstrated, but it has been established that in some of these diseases active infective agents are present in the circulating blood, or in the serum of local vesicular lesions, or in portions of diseased tissues. These agents can be made to pass through the pores of fine earthenware and collodion filters and their size thus determined by measurement of the pores of these filters—hence the term "filtrable viruses." A few have been successfully cultivated, but only in media containing living cells such as portions of chick-embryos. Injected into monkeys and some other susceptible animals, the virus multiplies, and the specific disease is reproduced, suggesting that the virus is a living agent. Barnard, using ultra-violet light and special quartz lenses, has been able to photograph very minute particles in infective fluids such as serum and tissue-extracts. The "**elementary bodies**" of smallpox and vaccinia were first recognised and demonstrated as long ago as in 1886–87 by our own old teacher, Dr. John B. Buist, Lecturer on Vaccination in Edinburgh University. He clearly differentiated them from bacteria, estimating their size at 0·15μ, and they should therefore undoubtedly be known as "**Buist's elementary bodies.**" Subsequently, in 1892–97, in connection with the same diseases, the intracellular **inclusion-bodies** formed by the aggregation of these elementary bodies were described in detail by Guarnieri as spherical in outline, eccentric in position in the cells and surrounded by a clear area with a ring of minute granules at its periphery—and hence they are sometimes known as "**Guarnieri's corpuscles,**" They were again, in 1906, described by Paschen as minute intracellular bodies 0·1 to 0·25 μ in diameter, and are therefore by some writers called "**Paschen's granules.**" From the work of Ledingham and others, it seems now established that these "**granules**" or "**elementary bodies**" are definitely the causal virus of vaccinia and variola, and Bland and Robinow (1939) hold that the inclusion-bodies are an obligatory stage in the multiplication of the virus and are colonies of elementary bodies enveloped in a matrix. According to Findlay (1939), when a virus becomes active within a cell, it produces one of two lesions. The cells may be stimulated to divide so that the tissues become hyperplastic; or they may be so severely damaged that necrosis ensues. Necrosis, however, may in many cases follow a primary hyperplasia. Examples of hyperplasia are the infective warts and certain neoplastic formations in man (pp. 287–9); whilst the necrotic processes are found in the liver in yellow fever, and in the ventral horns of the spinal cord in acute poliomyelitis.

When once the viruses have entered the body, they may infect the cells at the point of entry, as in warts, or may travel by the blood-stream, the lymphatics or by nerve-fibres to particular cells for which they are specially pathogenic, as in diseases such as rabies, poliomyelitis and yellow fever. The main portals of entry are the skin and mucous membranes.

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[1] Since this chapter was first written, we welcome the appearance of the book on "Virus Diseases of Man," by C. E. van Rooyan and A. J. Rhodes (University of Edinburgh), Oxford University Press, 1940. New discoveries in this field of pathology are still so constantly being made that, for accounts of the most recent of these, we must perforce refer our readers to current articles and papers in the medical journals.

[2] In the viral disease of potatoes, *e.g.*, "mosaic disease," the infection is carried by sap-sucking insects such as green-fly or aphides.

We do not propose to deal with the methods of demonstrating the filtrable viruses or of reproducing the related diseases in experimental animals and plants, but refer our readers to text-books on bacteriology and immunology, in which these methods are described. Some viral diseases are highly contagious, *e.g.*, foot-and-mouth disease, smallpox, and yellow fever.

It is now generally accepted that the following diseases are caused by filter-passing viruses—smallpox (variola) and cowpox (vaccinia), chickenpox (varicella), rabies, epidemic encephalitis (encephalitis lethargica), poliomyelitis and polio-encephalitis, myelitis in some of its manifestations, herpes, measles, yellow fever, psittacosis, mumps, influenza, the common cold, molluscum contagiosum, infective warts, lymphogranuloma inguinale, foot-and-mouth disease, canine distemper, and swine-fever. Mild or "**abortive**" forms of some of these viral diseases are now recognised, for example, in the case of poliomyelitis and epidemic encephalitis (pp. 105, 109); and it is not unlikely that other curious and puzzling epidemics of, for example, "persistent hiccough" (pp. 110–11), "epidemic nausea and vomiting" in schools (Miller and Raven, 1936; J. D. Gray, 1939), and other ailments at present labelled with the indefinite if convenient title of "influenza," gastric or otherwise, will similarly prove to be caused by viral infections, some of them "neurotropic," *i.e.*, attacking especially the nervous system (pp. 105 and 121).

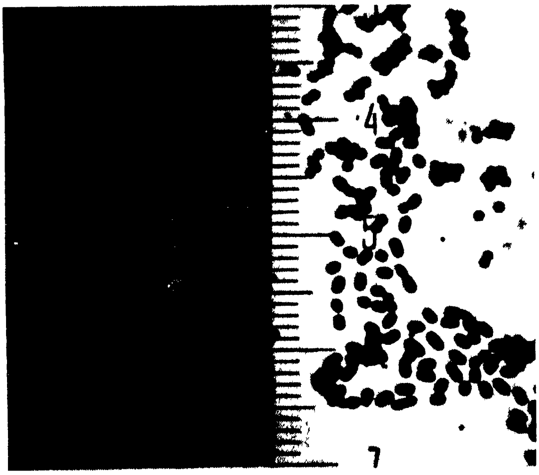

Fig. 54. Vaccinia virus-bodies (*left*): with staphylococci and *Bacterium coli* for comparison (*right*). × 1225. One small division = 1·14 μ. Paschen's basic-fuchsin stain for elementary bodies. (By courtesy of Dr. van Rooyen.)

Pathological Lesions. We shall deal here with the pathology of the more important of these diseases which affect man only, or are recognised as communicable from animals to man. Various attempts have been made to classify these viruses according to the tissues which they primarily attack, or according to the pathological changes associated with the various diseases to which they give rise, but our knowledge on this subject is still too meagre to render any classification of much scientific value.

For convenience of study, however, we adopt the following division into four groups.

Group I. Those in which the characteristic, but not necessarily the primary, lesion appears in the **skin**—smallpox and vaccinia, chickenpox, herpes, lymphogranulomatosis and foot-and-mouth disease.

Group II. Those in which the obvious lesion is in the **nervous system,** and especially in the **nerve-cells**—poliomyelitis and polio-encephalitis, epidemic encephalitis, ascending myelitis, equine encephalomyelitis, hydrophobia (rabies) and probably acute lymphocytic choriomeningitis.

Group III. Those in which the infection is more general and frequently characterised by **catarrhal lesions,** especially in the respiratory and intestinal tracts, but lesions in the skin and in the nervous system may also be present at some period of the illness. These general and catarrhal changes are seen in measles, yellow fever, psittacosis, the common cold, influenza, and to a less extent in mumps.

Group IV. Those which give rise to **tumours** or **tumour-like formations,** such as the "Rous sarcoma" and other sarcoma-like tumours, molluscum contagiosum, the "Shope-tumour" (p. 287), warts and possibly Hodgkin's disease.

Groups I and II resemble one another in their general characters and in their special association with ectodermal tissues, and, though members of Group I, in most instances, manifest their lesions particularly in the skin, and are therefore classed as **dermotropic,** they may also produce serious nervous conditions closely resembling the diseases produced by Group II.

Hurst classifies those viruses which primarily attack and destroy nerve-cells, but which do not usually give rise to any dermotropic lesions, as strict **neurotropes** (Group II). The virus in these cases travels from a peripheral site by way of the nerves, and seems to multiply only in nervous tissue, at all events in the early stages of the disease.

Those viruses which either do *not* produce nervous lesions in man or produce them only *late* in the disease, but which do give rise in susceptible animals to serious nervous involvement, he calls **pantropic** viruses. Thus herpes facialis in man is dermotropic, but, if the fluid from the vesicles is inoculated into the cornea of rabbits, it not only produces a local keratitis but often causes death with post-mortem evidence of a meningo-encephalitis; whilst subdural injection leads to the production of a rapidly fatal encephalitis. Yellow fever is included in this group, as nervous lesions tend to develop in the later stages of that disease.

Hurst's **viscerotropic** viruses, such as those of vaccinia and lymphogranulomatosis, do not spontaneously produce nerve-lesions, but if inoculated directly into the brain they give rise to primary meningitis with secondary damage to nerve-cells. Further, it has been shown that vaccinia-virus can be adapted to growth in cerebral tissue of living animals, and the occurrence of post-vaccinial encephalitis is regarded by some as due to the latent neurotropic tendency of the primary vaccinia-virus.

GROUP I

(Predominantly Dermotropic)

VARIOLA AND VACCINIA. In **variola** (smallpox) the initial stage is ushered in with a rigor. High temperature, pains in the back and limbs, vomiting, delirium, convulsions and other symptoms of general infection may be present. These symptoms are accompanied by an erythematous rash, chiefly on the lower part of the abdomen, the inner sides of the thighs, on the back and on the lateral aspects of the thorax. The rash may show as innumerable small hæmorrhages scattered over the body, but noticeable especially in the axillæ and groins. After three or four days, the initial eruption is replaced by reddish raised nodules—shotty to the touch—later becoming vesicular and containing clear serous fluid. These vesicles are multilocular in character (p. 101), and scabs are apt to form over them. If the condition subsides at this stage, the skin will show only brownish pigmented areas where the vesicles had been present. The fluid in the vesicles may become purulent, probably from secondary infection with staphylococci or other bacteria ; and from the pustules thus formed the lesions extend into the tissues in the immediate neighbourhood and produce the **confluent** type of the disease. In severe cases, the pustular eruption is often intense on the face and hands, scabs are formed and, after these are cast off, deep irregular scars remain. Sometimes hæmorrhages occur in the interior of the nodules or vesicles (**hæmorrhagic smallpox**). Besides the skin-eruption, pustules are sometimes formed on the mucous membranes of the mouth, tongue, nose, pharynx, larynx, trachea, œsophagus, conjunctiva and cornea. Bronchitis, pneumonia, intestinal catarrh, arthritis and nephritis are not uncommon complications.

Vaccinia. The virus of cowpox is undoubtedly identical with that of smallpox, but, owing to the modification in virulence of the virus by passage, the lesions in man are, in the vast majority of cases, localised to the area of inoculation. It is well-established that variola-virus, after passage through calves, loses its power of producing smallpox when inoculated into man, and is modified to such an extent that it may produce only a very slight local lesion. Serum from a case of smallpox will, on inoculation, protect against an attack of vaccinia, and it is common knowledge that serum from a vaccinia-pustule will protect against smallpox.

Post-Vaccinial and other Forms of Post-Infectious Encephalomyelitis. Although occasional cases of post-vaccinial encephalomyelitis were recognised during last century as early as 1860, it was only about 1922 that attention was called to its apparently slightly less rare incidence ; and occasional small epidemics have been reported, *e.g.*, in Great Britain in 1923. Although more than one case has sometimes occurred in the same family, no proof that the spread was by contact or contagion has been forthcoming, nor has the actual source of the vaccine-lymph itself been proved to play any obvious or important part in causation. It is not yet definitely known whether such post-vaccinial and post-variolar encephalomyelitis merely resembles, or is actually identical in nature with, the forms of the disease which follow anti-rabies inoculation and measles : or, indeed, the variety seen in cases of apparently spontaneously-occurring acute disseminated encephalomyelitis. In all of these, the naked-eye and microscopical changes in the central nervous system are so similar as to be practically indistinguishable. The brain and cord show congestion and œdema, and the histological findings, which vary with the stage or period of the disease at which death has occurred, are lymphocytic and plasma-celled perivascular infiltrations ; but the most characteristic phenomenon is the production of a zone of **acute perivascular myelinoclasis** or demyelination around the vessels,[1] giving a fenestrated appearance to the affected tissues, and, in suitably prepared sections, these zones are found to contain fat-laden phagocytic "foam-cells," situated both outside and inside the Virchow-Robin perivascular spaces. Some of these cells are probably microglial endothelial, others, in origin ; and they are engaged in clearing away the disintegrating myelin and other debris. Such inflammatory and destructive changes may be widespread throughout the whole central nervous system, or may be focussed especially in certain regions such as the lumbar enlargement of the cord, the pons, and the substantia nigra of the mid-brain.

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[1] "Acute Perivascular Myelinoclasis ('Acute Disseminated Encephalomyelitis') in Smallpox," by J. Pickford Marsden and E. Weston Hurst, Lister Institute, *Brain*, 1932, **55**, 181.

Post-vaccinial encephalitis occurs most commonly in persons in whom vaccination has been delayed till *after* the first year, being practically unknown in infants under that age. Though this form of acute disseminated encephalomyelitis may be a specific disease unassociated in its ætiology with vaccinia-virus, the view taken by some workers is that there is in the infected individual a "latent" neurotropic virus which is stimulated to activity by vaccination. On the other hand, there is much evidence in favour of the view that the actual causal agent is the vaccinia-virus itself. A similar encephalitis has been described as occurring in smallpox ; and vaccinia-virus has occasionally been demonstrated in the brain in cases of post-vaccinial encephalitis. By continued passage through the brains of rabbits, vaccinia-virus may acquire a special affinity for the tissues of the nervous system and be still able to produce the typical lesions of the skin.

Alastrim. This disease is characterised by an eruption similar to that of smallpox, but with very much less severe constitutional disturbance. The eruption consists of single-chambered vesicles which rarely suppurate. No scars are left, and there is practically no extension of the inflammation into the surrounding tissues. All the evidence seems to show that the virus of this disease is merely a variant of the variola-virus—a variant in which the toxic effects on man are mild, but its antigenic properties are practically unaltered.

The Nature of the Virus. Reference has already been made (p. 96) to Buist's elementary bodies and to the inclusions (Guarnieri's corpuscles) found in the cells of the lesions of vaccinia and variola. These elementary bodies can be obtained in a pure state by high-speed centrifugalisation, and a specific agglutination-reaction is obtained when they are suspended in anti-vaccinial serum. Using a strain of vaccinia-virus isolated from a case of alastrim, Rhodes and van Rooyen (1937) scarified the cornea of rabbits, three to six months old, and instilled into the conjunctival sac 0·1 c.cm. of a 1 in 10 broth-suspension of this virus. From the first day onwards they were able to demonstrate in the fibroblasts the presence of oxyphil inclusion-bodies, which, after careful investigation, they concluded were aggregations of elementary bodies and represented a phase in the growth of the virus. They noted also the presence of typical Guarnieri-bodies and small granules in the cytoplasm of the corneal epithelial cells. Control-experiments with mechanical, chemical and bacterial irritants gave no evidence of the presence of such inclusion-bodies. Similar experiments with rabbits immunised against vaccinia were also negative.

Pathological Histology. In cases of smallpox and vaccinia, areas of inflammation, widespread or localised, are present in the skin. Histologically, the picture is similar in the two conditions. In the early stages, an exudation of lymph and an infiltration of leucocytes occur and vesicle-formation takes place. The infiltrating cells are of both mononuclear and polymorphonuclear types. As already noted, the fluid in the vesicles is at first clear, but later becomes purulent, and at this stage the polymorphonuclear cells may be very numerous. The vesicles and, later, the pustules, in ordinary cases of smallpox and in vaccinia-inoculation, are situated in the epithelium. The superficial layers which form the roof of the vesicle show vacuolation and other necrotic changes, but the Malpighian layer may remain intact. Bridges of epithelium stretching from the degenerated surface-layer to the floor of the vesicle may divide it into irregular compartments. Later, the superficial epithelium becomes completely degenerated, the purulent exudate dries up and, as stated on p. 99, a scab is formed. When this scab is cast off, a small pit which has its walls lined by epithelium which has grown up from the basal (Malpighian) layer may be left. In severe cases, and especially in those in which secondary bacterial infection has occurred, the inflammatory reaction may have extended through the Malpighian layer of the epithelium and spread into the subepithelial tissues, resulting in a fibrosis which causes deep and permanent pitting. The microscopical appearances found in the mouth, nose and other situations mentioned on p. 99 are similar to those of the vesicles in the skin, and may result in the production of small ulcers.

Nodules arising from focal infiltration by mononuclear and other cells and sometimes associated with necrosis may be present in the testes and bone-marrow ; and in the liver and kidney cloudy swelling is common and focal necrosis occasionally present. The spleen is usually enlarged. The necrotic element in these lesions is, in all probability, due to secondary bacterial infection and not to the virus of smallpox. Pathological changes in the central nervous system are described under encephalomyelitis (p. 99). Elementary bodies are seen in sections from the lesions.

After careful comparison of the lesions following cutaneous, intradermal, subcutaneous and intravenous inoculation of vaccinia-virus in animals, Ledingham (1924) concludes that the lesion is essentially an " acute infective granuloma in which the reticulo-endothelial system is primarily and dominantly involved."

" **Orf** " or **Contagious Pustular Dermatitis of sheep,** shown by Aynaud (1921) to be due to a filtrable virus, is communicable to man, in whom, usually on the skin of the hands or occasionally of the face, it produces a painless dark-red papule, generally single, which gradually develops to form a hard raised molluscum-like mass, 1 to 3 cm. in diameter, tending to become button-shaped and umbilicated, and lasting several weeks. The discharge, at first serous, becomes purulent and then gradually dries up, the lesion in its course and character bearing some resemblance to vaccinia.

HERPES SIMPLEX or **FEBRILIS** (**Symptomatic Herpes**) is characterised by the presence of small vesicles seen frequently at the junction of the skin and mucous membrane of the mouth or nostrils in patients suffering from febrile diseases such as pneumonia. Similar eruptions may occur elsewhere on the face (herpes facialis), cornea and genitalia (herpes genitalis). If the fluid from the vesicles on the skin is inoculated on the scarified cornea of rabbits, a severe herpetic keratitis may be produced. The fluid taken from this keratitis will produce typical herpes in the skin or cornea of man. The virus from this variety of herpes has only relatively slight neurotropic action in the human subject—transient mild encephalitic symptoms are occasionally observed[1] —but, in a susceptible animal, nervous lesions are common. A certain proportion of rabbits inoculated on the cornea develop an encephalitis which is characterised by degeneration of nerve-cells, infiltration of lymphocytes and plasma-cells into the brain-substance, and some proliferation of glial tissues ; and mice can also be successfully inoculated intracerebrally from the rabbit's eye. The virus is present in the vesicular fluid in the form of elementary bodies, and is demonstrable as minute granules which are both intra- and extra-cellular After infection, the virus apparently remains latent in the tissues, and, in such cases, although virucidal immune-bodies are also present in the blood, recurring attacks of herpes [1] may be precipitated by non-specific factors such as " colds," pneumonia, meningococcal meningitis, menstruation, the injection of heterologous sera, and the administration of certain drugs such as arsenic, etc. This form of herpes differs from the zoster type in being **recurrent**, irregular in its distribution and showing no cellular changes in the spinal fluid.

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[1] " Symptomatic Herpes, a Sequela of Artificially Induced Fever," by S. L. Warren, C. M. Carpenter and Ruth A. Boak, Rochester, N.Y., *Jour. Exper. Med.*, 1940, **71**, 155.

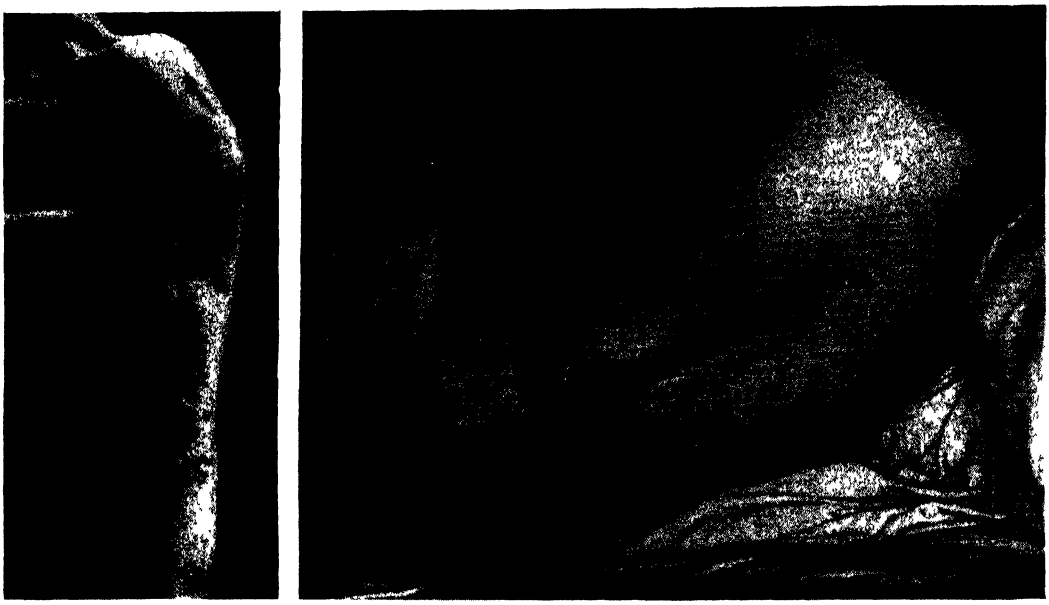
(A) (B)

FIG. 55. *Herpes Zoster.*

(A) Zoster brachialis in a male rubber-worker aged 60, showing the eruption in the vesicular stage. (A case of the late Prof. Greenfield.) (B) Zoster in a middle-aged male showing the girdle- or belt-like distribution. The vesicles are drying up to form scabs. (A case of the late Dr. Alexander Bruce.) For the lesions found in the spinal ganglia in a patient suffering from chickenpox, and in whom herpes zoster developed, *see* Fig. 55A in Appendix, p. 1260.

HERPES ZOSTER (**Zona, Posterior Poliomyelitis** or **Shingles**).[2] This is a specific infectious disease in which, following an acute inflammatory lesion of the **dorsal** or **posterior-root ganglia,** vesicles larger than those seen in herpes febrilis develop on the third or fourth day of the illness, most frequently on the trunk and confined to one side of the body and in the area of skin corresponding to the distribution of the sensory branches, especially of the intercostal nerves. The **Gasserian ganglion** may be attacked and the eruption then appears in some part of the cutaneous distribution of the trigeminal nerve—the ophthalmic division being most commonly involved, **ophthalmic zoster.** Vesicles may develop on the cornea. More rarely, the third cranial nerve is attacked, with resulting oculomotor paralysis. Zoster-vesicles sometimes appear on the pinna of the ear, the anterior pillar of the fauces, the soft palate or tongue as a result of involvement of the **geniculate ganglion** of the seventh cranial nerve.

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[1] " Recurrent Traumatic Herpes," G. M. Findlay and F. O. MacCallum, *Lancet,* 1940, **i**, p. 259.

[2] Greek ἕρπειν, *herpein,* to creep along and to spread ; ζωστήρ zōstēr, a girdle or belt. The popular term " shingles " is derived from the Latin *cingulum,* a belt (*see* Fig. 55, B, above).

The lesion is preceded and accompanied by severe neuralgic pains along the course of the affected nerve-branches. Though **oxyphil inclusion-bodies** have been described in the nuclei of the cells of the vesicle-epithelium by Bedson (1930), the disease has not been transmitted to experimental animals by inoculation with the fluid from these vesicles. There appears to be a definite association between zoster and chickenpox and a frequent sequence is an attack of zoster in an individual, followed after some ten days by varicella in a contact ; and many observers (Russell Brain, 1933 and 1940) are of opinion that the virus of both diseases is similar, if not identical (*see* Fig. 55A in Appendix, p. 1260).

In the **cerebrospinal fluid,** the cell-count is variable, but, during the active stage of the disease, up to 100 cells or more per c.mm., almost exclusively lymphocytes, or these along with some larger mononuclears, are found, together with, in some instances, a rise of total protein up to perhaps about 100 mgr., though in other cases the protein, along with sugar and chlorides, may remain normal in amount. The pleocytosis may persist for weeks or months after the disappearance of the skin-eruption (Henry Head).

The **pathological changes** in the affected dorsal root-ganglia are acute inflammatory in nature. To the naked eye, the ganglia appear swollen and congested and may show petechial hæmorrhages. Microscopically, there is small round-celled infiltration, especially in the form of perivascular cuffing, in their substance and capsules. Numbers of the ganglion-cells show varying stages and degrees of degeneration up to complete necrosis, followed by their disappearance. Secondary degenerative changes and subsequent sclerosis ensue, not only in the affected ganglion itself, but in the corresponding afferent fibres of the sensory nerves going to the ganglion and in the fibres passing from it into the cord, more particularly in the ascending tracts of the dorsal columns. Similar changes occur in the trigeminal (Gasserian) ganglion of the fifth and in the geniculate ganglion of the seventh cranial nerve when these are attacked by the disease. In rare instances, the lower motor-neurone cells are attacked, probably by a spread of the inflammation from the cells of the dorsal horn to those of the anterior horn of the spinal cord, with resulting atrophic muscular paralysis (Russell Brain, 1940). Ocular and facial paralyses are due to inflammation of the fifth and seventh cranial nerve-trunks. Rarer manifestations of zoster may occur in connection with joints (zoster-arthritis), the pleura, pericardium or abdominal organs (visceral zoster), or by extension of the inflammation from the neuraxis to the leptomeninges (zoster-meningitis), or as a complication in the substance of the brain itself (zoster-encephalitis).

Biggart and Fisher (1938) report a case of zoster-meningo-encephalitis in which there was mononuclear infiltration of the subarachnoid space especially over the posterior aspect of the cord, a perivascular lymphocyte-infiltration in the medulla, subcortical cerebellar nuclei, the thalamus and hypothalamus and to a less extent in the cord. There was a diffuse increase of cells in the posterior or dorsal horns and varying degrees of chromatolysis in the nerve-cells. The dorsal root-ganglia showed the characteristic pathological changes associated with herpes zoster.

VARICELLA or **Chickenpox.** In the fluid from the vesicles, coccoid bodies occurring singly or in chains have been demonstrated, and growth in tissue-culture has been obtained. The inoculation of animals with material from the skin-vesicles of definite cases of varicella has generally given negative results. As noted above, many observers, mainly on clinical grounds, consider that herpes zoster and varicella are caused by closely allied, or possibly identical, viruses (*see* Appendix, p. 1260). Serum from patients convalescent from varicella agglutinates the zoster elementary bodies and *vice versâ.* A disseminated or patchy form of encephalomyelitis complicating chickenpox has been described by van Bogaert (1932) and others.

LYMPHOGRANULOMA INGUINALE, LYMPHOPATHIA VENEREA or **Climatic Bubo** (p. 755). This disease, which is spread by sexual contact, starts in the case of males as a small lesion at the site of inoculation on the penis, and this is followed by a subacute inflammation of the inguinal lymph-nodes. **Microscopical examination** of this initial lesion reveals a granulomatous condition containing various types of histiocytes, many of them multinucleated, this type of cellular reaction, however, being in no way specific for this disease. The lymph-nodes tend to suppurate and chronic sinuses are produced, but the initial lesion soon heals and males then cease to be infective. In females, however, if the primary lesion is situated at the posterior region of the genitalia, there is a tendency for the condition to spread by lymphatics to the ano-rectal tissues, producing chronic inflammatory and ulcerative changes in them, possibly with stricture of the anal canal and ulceration of the vulva—a condition referred to as "*esthiomène.*" Such changes lead to persistent infectivity. The causal virus is filtrable, and subcutaneous inoculation of the filtrate into monkeys gives rise to the typical disease. Similarly, experimental inoculation has produced the disease in man. Intracerebral injection in monkeys gives rise, after an incubation-period of six to twelve days, to a meningo-encephalitis. Elementary bodies have been demonstrated by Miyagawa (1935) within the cells of the infected lymph-nodes and in the lesions in the brain. Frei (1925) showed that in infected individuals a reactive inflammation of the skin follows in twelve to twenty-four hours at the site of intracutaneous inoculation of sterilised pus from a typical bubo. There is no reaction in non-infected patients.

FOOT-AND-MOUTH DISEASE. This highly infectious disease attacks cattle, sheep, goats, pigs, and other animals, and is capable of transmission to man. In Great Britain, it is most prevalent in autumn and winter, and starlings have been suspected as being concerned in its spread. The characteristic lesion in cattle is a vesicular eruption on the feet and in the mouth. With the serous exudate from these vesicles, the disease can be reproduced experimentally in cattle. The serum is infective even after filtration through fine filters, and the virus has been grown in a tissue-culture-medium made from the foot-pads, lips and skin of embryo guineapigs. In the human subject, vesicles may appear on the mucous membrane of the lips, and mild cases of stomatitis in young children are said to be caused occasionally by the virus in infected milk.

GROUP II

(Predominantly Neurotropic)

ACUTE ENCEPHALITIS and ENCEPHALOMYELITIS (p. 1049). Various types of this disease occur in man and in the lower animals, all characterised by an inflammatory reaction and damage to nerve-cells. Some cases are bacterial in origin, but the great majority are caused by some variety of virus. In the early stages, the exudate may show varying numbers of polymorphonuclear leucocytes, but in general the cells of the accompanying infiltrations and exudates, and also the cells which find their way into the cerebrospinal fluid from these, are mononucleated and principally of small-lymphocyte type. In some instances, "inclusion-bodies " occur in the nuclei or in the cytoplasm, or in both situations, and these bodies are now commonly regarded as particles or colonies of virus. As has already been stated, certain of these viruses are **neurotropic,** and to this type belong those which produce the various forms of **acute encephalitis** and **encephalomyelitis.**

ACUTE ANTERIOR POLIOMYELITIS and POLIO-ENCEPHALITIS (Infantile Paralysis) (p. 1049). According to American workers, this disease is widespread, but it is only in a small proportion of cases that the paralytic symptoms develop. As it has in the past been especially upon this later paralytic stage of the disease that attention has been focussed, the **non-paralytic** and **pre-paralytic** cases (in which there may be spasmodic contraction—not paralysis—of the muscles) have until comparatively recently often escaped recognition. Antibodies capable of neutralising and protecting against the virus of poliomyelitis have been found to be present in the blood of a considerable proportion of healthy persons, and it is not unlikely that they have acquired this immunity by having previously been exposed to and contracted the infection in one of its commoner and milder forms, no paralysis having occurred to call attention to the true nature of the disease which had, therefore, not been recognised at the time of the attack. As implied by the term " infantile paralysis," those most commonly infected are infants, usually between the ages of two and four years, and, though no age is entirely exempt, children of school age are also liable to attack, either sporadically or in epidemics, *e.g.*, in schools and institutions. In adolescents and adults, especially in country districts—in the towns they are more likely to have developed immunity from having had some previous slight attack or series of attacks of the infection—the results of the disease are often more serious than in children. Aycock and Luther [1] (1929) have reported 16 cases in which poliomyelitis developed during the second and third weeks after tonsillectomy, and they therefore suggest that the raw surface so produced had been the probable portal of entry in these cases. In another epidemic occurring in a school, Scott-Brown [2] reported 15 cases of polio-encephalitis affecting the brain-stem, every case having previously suffered from a pharyngitis or tonsillitis, and the apparently case-to-case infection having been thus probably carried to the central nervous system by the vagus or glossopharyngeal nerves. It has been suggested that it is especially by way of the non-medullated nerves that the virus enters and travels, and that, apart from trauma, it can obtain access to these, not only through the olfactory or naso-pharyngeal mucosa, but also through the mucous membranes of the

[1] *New England Journal of Medicine*, 1929, **200**, 164.

[2] *Lancet*, 1931, ii, 1287.

respiratory and gastro-intestinal tracts, and so reach the sympathetic or parasympathetic nerves and plexuses in their walls.

Some of the symptoms of the disease mentioned by Weston Hurst (1935) are : (1) disturbance of sleep-rhythm—sleepiness by day and restlessness by night : (2) general hyperæsthesia to every touch and passive motion : (3) sweating, flushing, disturbed intestinal peristalsis, and tachycardia. The temperature frequently reaches 103° or 104° F.

From the damaged nervous and other tissues a filtrable virus has been obtained, which, when inoculated on the scarified mucous membrane of the nose of monkeys, has reproduced the infection. Similar positive results have been obtained by injection of emulsions of the diseased tissues directly into the brain. From the nasal mucous membrane it is thought that the virus travels along the olfactory nerves—probably by way of the axis-cylinders, *i.e.*, along the interior of the medullary sheaths of these as within a tube—to the olfactory bulbs (though no pathological changes have yet been detected in these) and then from nucleus to nucleus until it reaches the motor cells in the ventral (anterior) horns of the spinal cord. These motor cells show varying degrees of degeneration, from slight chromatolysis to actual necrosis, and Wallerian degeneration follows, with resulting lower-neurone flaccid paralysis.

At a comparatively early stage in this passage of the virus from the olfactory mucosa (if that be the site of entry) to the motor-cells in the cord, it reaches and involves the important nuclei in the hypothalamic region, producing degenerative changes in the nerve-cells. It has been suggested by Faber (1933) and others that many of the symptoms occurring in the early stages of the disease can be referred to such lesions in the thalamus and the hypothalamic region. It is claimed that the virus has been recovered from the spleen and the mesenteric lymph-nodes at a late stage in the disease, and that it has also been found in the cerebrospinal fluid in some cases, probably as a result of the involvement of the meninges which has followed upon the preceding infection of the motor-cells of the ventral horns. The virus is obtained most abundantly and easily from the substance of the cord in the affected regions, but it is present also in the naso-pharynx, tonsils and associated lymph-nodes of persons suffering from the disease, not only in its paralytic but also in its earlier and milder forms. In the nasal secretions of healthy persons in contact with infected patients the virus has been found ; and there seems little doubt that in many cases the infection has its original site in the upper respiratory tract ; though in some, as already suggested, it may be gastro-intestinal ; and monkeys have now, in Australia (1940), been infected by oral administration and the virus recovered from their mesenteric lymph-nodes. Similarly, experimental evidence has been brought forward [1] suggesting that the virus of poliomyelitis is present in the fæces of patients during the earlier (active) infective period of the disease ; and that the infection may thus be spread by the contamination of drinking-water or milk and other foods with excreta—for example by earth-contaminated strawberries—or by flies. For these experiments, the fæcal material was treated with volatile antiseptics such as ether or acetone, rather than by the usual method of filtration by which the concentration of the virus is likely to be insufficient to produce infection when injected into monkeys.

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[1] Trask, Vignec and Paul (1938), quoted by Kling, Olin, Magnusson and Gard, *Bull. Acad. Med.*, June 13th, 1939, p. 826 (quoted in *Brit. Med Jour.*, 1939, ii, 753). See also *Lancet*, 1939, ii, 893; and *Brit. Med. Jour.*, 1940, ii, 711, and 1941, ii, 311.

The virus has (1939) in America been successfully isolated from sewage in districts where epidemics of poliomyelitis had occurred, and (1940) from the sewage of hospitals in which cases of poliomyelitis were being treated.

Pathological Changes. On naked-eye examination, irregular areas of congestion of the ventral horns and perhaps also of the leptomeninges may be present, and, occasionally, small patches of hæmorrhage and softening in the substance of the cord. On **microscopical examination**, when the paralytic stage of the disease is established, the characteristic lesions are found in the grey matter of the cord, mainly in the ventral horns, especially in the region of the lumbar and cervical enlargements. In the grey matter, an infiltration of the perivascular sheaths—" cuffing "—of the vessels, similar in character to that found in other myelo-encephalitic viral infections, occurs, and is associated with a diffuse cellular invasion of the grey matter (Figs. 56 and 57)—the cells being of the same types as those found later in the membranes. All stages of cellular degeneration, from a slight degree of chromatolysis up to complete destruction of the motor nerve-cells of the ventral horns, can be seen (Fig. 638, p. 1048). The vessels may be thrombosed, and irregular areas of hæmorrhage are not uncommon. The distribution of the degenerative lesions is often irregular, and apparently unaffected nerve-cells may be found in the immediate neighbourhood of necrotic areas. The myelin-sheaths and axons of the damaged cells also undergo descending degeneration and disintegration. In some acute cases, necrosis may be considerable and the leucocytic reaction slight. Experimental evidence supports the view that degeneration of the nerve-cells *precedes* the vascular changes and any perivascular reaction or cellular infiltration in the meninges. In severe cases, the evidences of such leptomeningitis may be more pronounced, with infiltration of the sheaths of the nutrient arteries, especially those situated anteriorly (ventrally), with cells mainly of the mononuclear variety—

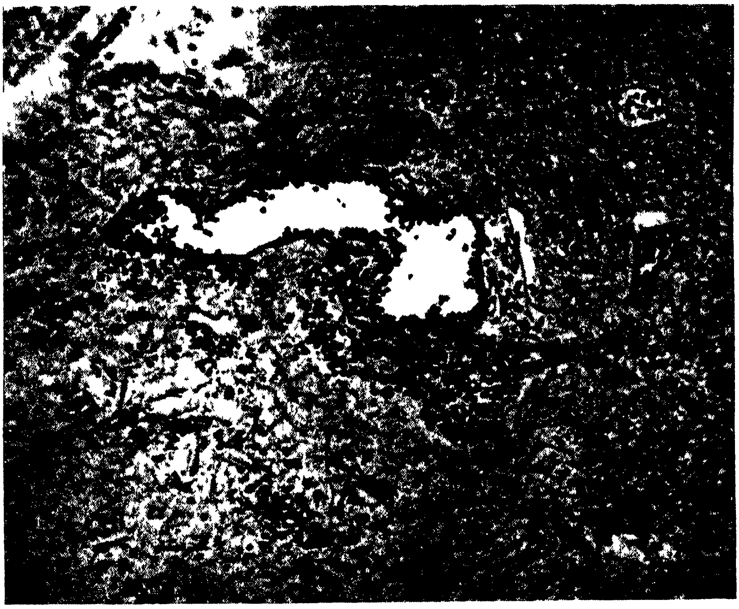

FIG. 56. *Acute Anterior Poliomyelitis.* Section of ventral horn of cord, showing perivascular " cuffing," œdema, etc. (see text). Hæmatoxylin and eosin. × 150.

lymphocytes and a few plasma-cells—but varying numbers of polymorphonuclear leucocytes are also present.

The lesions in the spinal cord are associated with similar, but as a rule less intense, degenerative changes in the nerve-cells in certain foci in the cerebrum, especially in the thalamus and hypothalamic region, and in the medulla: in the last-mentioned position, if severe, producing clinically the symptoms of **acute bulbar paralysis.** Turnbull and McIntosh [1] (1926) have also described lesions reaching as high as the basal ganglia and even the cerebral cortex. In other cases again, the virus when it reaches the motor-cells of the cord may cause damage first at its lower part, *e.g.*, in the lumbar enlargement, and then spread rapidly upwards, producing one type of **Landry's acute ascending paralysis** (pp. 116 and 1167 *et seq.*). In this connection it is of interest to note that the disease when produced artificially by injection of the virus into a nerve, *e.g.*, the sciatic of one limb, attacks first the motor-cells of the ventral horn of the same side at the level in the cord corresponding to its nerve-cell origin, *i.e.*, the nerve-cells from which the axons of the nerve are derived. From these ventral-horn cells the infection may then spread, both by contiguity and continuity, by way of nerve-fibres within the central nervous system and may ultimately even reach the corresponding pyramidal motor nerve-cells of the cerebral cortex on the opposite side of the brain.

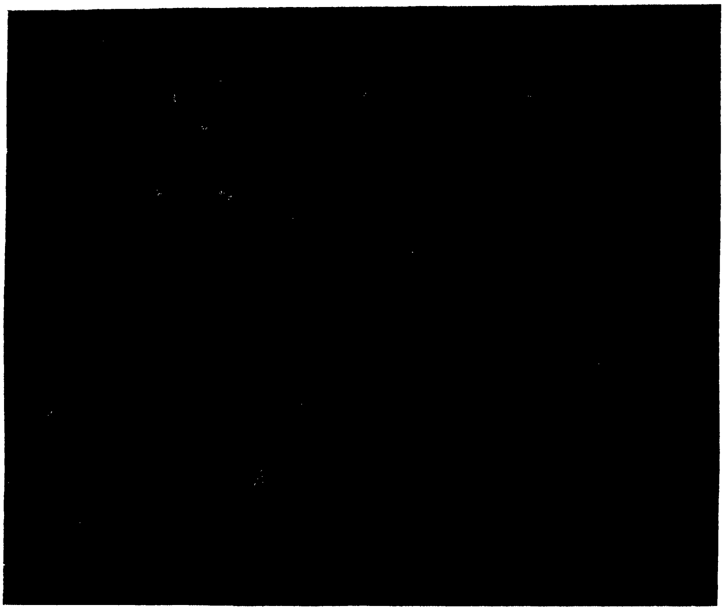

FIG. 57. *Acute Anterior Poliomyelitis.* Paraffin section of ventral horn during acute stage of disease, showing œdema and numerous emigrated polymorphs. Hæmatoxylin and eosin. × 300.

The paresis or paralysis of muscles varies according to the severity of the spinal lesion, and its distribution is in relation to the myotomes or groups of muscles supplied by the affected segment or segments of the cord—single muscles alone being rarely involved. The paralysis is typically of flaccid or lower-neurone character, and certain muscles are more liable than others to be picked out, for example, in the case of the lower limb, which is affected in three-quarters of the cases, the quadriceps femoris, peronei, flexors of the ankle and extensors of the toes : or, in the case of the arm, in less than half of the cases, the deltoid being often paralysed, perhaps along with some of the scapular muscles and those which flex the elbow and supinate the forearm. Muscles of the trunk are attacked in about a quarter of the cases, and, in fatal cases, death results most commonly from involvement of the respiratory muscles, including the diaphragm. The motor nuclei of cranial nerves may be picked out in just over a tenth of the total cases, the corresponding order of frequency of attack being the facial muscles, the muscles of deglutition, then the extrinsic muscles of the eye, and least frequently those which move the tongue and lower jaw.

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[1] *Brit. Jour. of Exper. Pathology,* 1926, **7,** 181.

Results. The acute symptoms may pass off in a few days, and, unless the destruction of the nerve-cells has been extensive, a considerable degree of recovery is possible. If the damage has been severe, small irregular necrotic cavities may sometimes be formed (p. 1163). The microglial cells become amœboid and take up lipoid debris and thus the degenerated material is absorbed : the neuroglial cells proliferate and gradually the affected parts shrink —the ventral horn atrophies and the ventral nerve-roots become wasted : and Wallerian degeneration and overgrowth of the interstitial neuroglial tissue follow (Figs. 639 and 640, p.1050). The corresponding muscles undergo atrophy of their fibres, which are replaced by connective tissue, and, as a result of the unopposed action of muscles which are not involved, deformities such as club-foot may thus be produced. The bones of the affected limbs may show atrophic changes and impaired growth and development (p. 1051).

Cerebrospinal Fluid. In the pre-paralytic stage of the disease, an increase of cells, up to and even exceeding 500 per c.mm., with a predominance of polymorphonuclear leucocytes is found, and a fine "spider-web" fibrinous coagulum may form in the specimen on standing. Later, there is a gradual fall in number and an alteration in the type of cell—the lymphocytes predominating even as early as the fifth or sixth day from the onset of the disease. In the paralytic stage of the disease the fall is rapid, and in a week there may be only 50 per c.mm. and in a month about 5 cells. Coagulable protein may at first show no, or only a moderate, increase, but a rise to 100, 200, or even 300 mgr. (0.1 to 0.3 per cent.) may occur during the first few weeks, with a subsequent fall and return to normal in six weeks. The sugar-content is normal and the chlorides are usually within normal limits or occasionally slightly lowered. The colloidal-gold curve may be of mid-zone type, but the rise is usually only slight or moderate and the level returns to normal in the later stages of the disease.

EPIDEMIC ENCEPHALITIS (**"Encephalitis Lethargica"** or **"Sleepy Sickness"**—p. 1052) (**Type A**). Although one of the names in common use for this condition is "encephalitis lethargica," suggested in 1917 by von Economo in connection with the Vienna outbreak of the disease, by no means every case is necessarily of **lethargic** or **akinetic** type. A proportion of patients attacked exhibit **hyperkinetic** symptoms, and (although the incidence of the disease is not infrequently sporadic) we prefer to use the term **epidemic encephalitis,** now employed by most writers, as less likely to mislead our readers.

In this disease, which, as the first of the above names implies, may occur in **epidemic** form, the symptoms and corresponding distribution of the pathological findings are remarkably variable, not only in individual cases, but in different epidemics.

Ford (1937) distinguishes the following types of acute epidemic encephalitis, the names of which are self-explanatory, but it must be added that all intermediate varieties and admixtures are found :—

(1) The **somnolent-ophthalmoplegic** *type or so-called "* **sleepy sickness,** *" in which the pathological process is most intense in the mid-brain and hypothalamic region.*

(2) The type marked by excitement and delirium and involuntary movements, often called the **hyperkinetic type**, with the lesions especially in the corpus striatum and diencephalon.

(3) The form characterised by early development of symptoms of the **Parkinsonian syndrome** which, however, is more characteristic of the chronic phases of the disease.

(4) **Fulminating** cases, occurring especially about the peak of an epidemic, and sometimes causing death, *e.g.*, from bulbar paralysis, within twelve hours or even less.

(5) **Abortive** cases, often mistaken for "influenza," but liable to be followed, although perhaps not till several years afterwards, by the development of the progressive Parkinsonian syndrome.

The sex-incidence of the disease is about equal. No age-period is immune from attack, but children and adolescents, especially in the second decade of life, and more particularly between the ages of fifteen and twenty years, are most liable to be affected.

Cases occurring in recent years tend to show symptoms very different in degree and even in kind from those of the earlier 1917, 1918, and subsequent epidemics (over 12,000 cases were notified in England and Wales between 1919 and 1925, nearly half of these being in the year 1924), in which acute and fulminant cases were common, the acute stage now tending to be much less severe and indeed often so inconspicuous as to be overlooked or regarded merely as a " cold " or a " touch of influenza," but followed after an interval of perhaps several months or even years by the Parkinsonian syndrome and other symptoms of the disease now established and become chronic. These phenomena should thus *not* be designated "*post*-encephalitic " or regarded merely as "*sequelæ*," as they are in reality part of the now chronic and still progressive disease itself.

No single symptom is pathognomonic, but those most characteristic of the acute stage are headache, some degree of pyrexia, visual abnormalities (such as double vision, usually associated with some variety of ophthalmoplegia—paresis or paralysis of the ocular muscles from neuritis or nuclear lesions affecting the sixth, third, or less frequently the fourth, cranial nerves) : facial weakness from involvement of the seventh nerve : attacks of myoclonus or spasmodic contractions of the muscles of the throat, diaphragm (hiccough) or limbs. There is frequently (especially in children) disturbance or inversion of the sleep-rhythm, with " sleepiness " or " lethargy " during the day and restlessness at night, sometimes prolonged periods of abnormal wakefulness, and in severe cases delirium or stupor or alternations of these. Extra-pyramidal disturbances may also occur in the acute stage, but are more typical of the later chronic progressive course of the disease. In addition to the foregoing symptoms, general and local, there are, especially in these later stages, the " Parkinsonian " immobile, mask-like facies and characteristic attitude of body and limbs and abnormalities of gait, with slowing and impairment of both voluntary and automatic or emotional muscular movement, rigidity, rhythmic tremor and movements akin to those of paralysis agitans, due to involvement of the corpus striatum, and/or of the substantia nigra of the mid-brain (p. 1072). Though the patient, when attempting to carry out the more ordinary movements, may be described as " muscle-bound," there is sometimes a curious capacity of performing quick rapid motions requiring a distinct effort, the so-called " kinesia paradoxa." There is not necessarily any mental disorder or impairment, but a change in the patient's normal emotional disposition and a loss of moral sense occur not infrequently, especially among children. Involvement of the hypothalamic nuclei and other parts of the autonomic system may produce metabolic and endocrine disturbances, for example excessive sweating and seborrhœa, respiratory and other abnormalities such as persistent hiccough and obesity or cachexia. Persistent hiccough, apparently of this nature, occurring in epidemics either during actual outbreaks of encephalitis or sometimes independently of these, is now believed to be a symptom of an abortive form of the disease (p. 97).

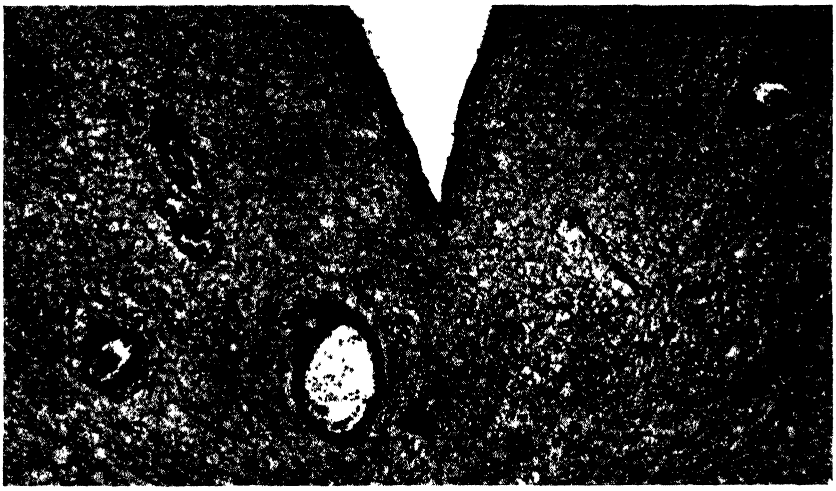
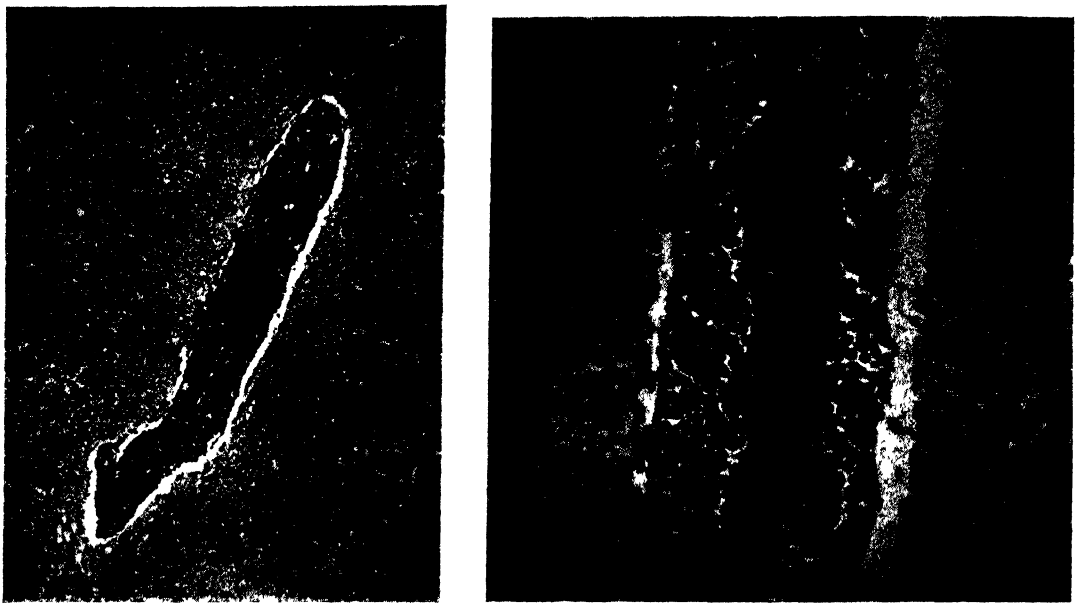


FIG. 58. *Acute Epidemic Encephalitis* (encephalitis lethargica). A low-power view of a paraffin section of the floor of the fourth ventricle, showing "cuffing" of small lymphocyte-like cells around the vessels. The ependymal lining of the ventricle is seen at the centre of the upper margin. Hæmatoxylin and eosin. (W. E. H. case.) × 100.

Ætiology. It is claimed that the cause of epidemic encephalitis is a filtrable virus, but, although this is almost certainly true and though some observers maintain that the disease has been reproduced in rabbits and monkeys by intracerebral inoculation, the evidence is not yet quite conclusive, and other workers have so far failed to transmit the disease by experimental methods. It has also been established (McCartney, 1924) that a similar encephalitic disease occurs spontaneously in rabbits, and consequently the histological findings described as brought about by experimental infection of these rodents must still be regarded with a certain degree of caution, in spite of the fact that some of the apparently positive experimental results have otherwise been carefully controlled.

Pathological Changes. In fatal cases, post-mortem examination may, to the naked eye, show merely some congestion of, and small hæmorrhages in, the meninges, especially over the pons and medulla. An inflammatory reaction, *i.e.*, actual meningitis, may be present, but is usually not pronounced. Slight congestion with some œdema occurs in the grey matter of the mid-brain and in the substantia nigra. The main lesions found on microscopical examination are an infiltration of the meninges and cerebral tissues with mononuclear cells of lymphocytic and plasma-celled type and irregular nerve-cell degeneration. The blood-vessels show intense congestion, sometimes with hæmorrhages into their sheaths and into the surrounding tissues (Fig. 641, p. 1052). The leucocyte-infiltration is pronounced in the perivascular spaces and in the walls of the blood-vessels—particularly the capillaries and minute venules—forming a distinct sheath or " cuff " round the vessel (Figs. 58 and 59). The nerve-cells in scattered areas show chromatolysis and other stages in the degenerative process. The presence of phagocytic cells which ingest the remains of the degenerated tissue is common, and softened patches may occur in the neuroglia.



(A) × 85. (B) × 290.

Fig. 59. *Epidemic Encephalitis* (encephalitis lethargica).

Another low-power photograph, showing the small-round-celled " cuffing " in the Virchow-Robin space around the small cerebral capillary, the endothelial outlines of which are faintly stained at the periphery of the lumen which is filled with serum or plasma only.

High-power of the same vessel, showing details of the perivascular " cuffing."

Hæmatoxylin and eosin.

In the later stages of the acute process, and in the chronic phases of the disease which follow these or supervene in the mild or abortive cases, the brain-tissue shows chromatolytic and other degenerative changes in the affected nerve-cells, with actual destruction of some of the cells, their invasion by phagocytes (neuronophagy) and their ultimate disappearance. These phenomena in the nerve-cells are accompanied and followed by proliferation of neuroglia, and the perivascular lymphocytic infiltration persists. Such degenerative, necrotic and other changes are seen in the pons and medulla, especially in the floor of the fourth ventricle (Fig. 58), and in the basal ganglia and cerebral cortex. The lesions with which the Parkinsonian syndrome is usually associated, and to which it is now generally attributed, are the foregoing degenerative changes in the nerve-cells of the substantia nigra of the mid-brain lying between the tegmentum and the basis pedunculi, and possibly also in the cells of some of the other nuclei in this region. The muscular rigidity which is often a pronounced feature of the disease is due probably to the degenerative changes in the substantia nigra interrupting the extrapyramidal fibres from the globus pallidus which pass downwards to communicate with the lower motor neurones in the spinal cord. The occurrence of nerve-degenerations in the uncus, the roof of the mesencephalon and other situations has been described in detail by Spatz (1927).

Cerebrospinal Fluid. Changes in this are, at any stage of the disease, usually slight. There may be either no increase or only a moderate mononuclear pleocytosis of from 10 to 100 or 150 cells per c.mm., predominantly small lymphocytes (90 to 95 per cent.), with a few larger mononuclear and plasma-cells, polymorphonuclears being uncommon except early in the acute stage. Similarly, the amount of protein may be normal or only slightly increased, together with a trace of globulin in excess. We are not able to confirm the presence of any constant abnormal excess of sugar described by some writers, nor have we found any diminution in chlorides, both of these points being of importance in the differential diagnosis of epidemic encephalitis from tuberculous meningitis (p. 995). In the chronic stages of the disease the findings are usually negative or nearly so.

ST. LOUIS ENCEPHALITIS (Encephalitis B). This type of encephalitis which occurred in epidemic form in St. Louis in 1933, and again in 1937, and also in Kansas City and elsewhere in the U.S.A., was indistinguishable both in its clinical and pathological aspects from the cases recorded in the epidemic in Japan in 1924, and the late J. R. Perdrau [1] found the two viruses to be "antigenically similar when examined by means of hyper-immune sera." It resembled also in its pathological lesions those seen in encephalitis lethargica, attacking especially the basal ganglia, but in its symptomatology somnolence was uncommon, the oculomotor palsies and meningeal involvement were absent and the Parkinsonian syndrome infrequent. Serologically it was specific and immunologically distinct from the Japanese type, and from encephalitis lethargica and poliomyelitis. Nerve-cell destruction was intensive and widespread. Perivascular infiltration with mononuclear cells and aggregations of similar cells surrounding areas of damaged nerve-tissue were constant features. These degenerative changes were found in the cortex, the basal ganglia, the thalamus and hypothalamic region, and in the spinal cord. In cases investigated by Boyd, no special pathological changes were found in the mid-brain. Although the virus of this infection is distinct from that of "Western" equine encephalomyelitis (p. 114), the geographical and seasonal incidence of the two diseases largely coincide on account of the fact that they have a common insect-vector, *Culex tarsalis.*

AUSTRALIAN X DISEASE. This type of acute encephalomyelitis, characterised by varying degrees of nerve-cell destruction and perivascular infiltration by lymphocytes —lesions resembling those of "**louping-ill**" in sheep—has been produced experimentally by inoculation of the virus in the monkey, horse, calf and sheep. Perdrau (1936) considered it probable that infection is conveyed to man from the sheep.

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[1] *Jour. Path. and Bact.*, 1940, **50**, 545.

EQUINE ENCEPHALOMYELITIS [1] is a disease practically confined to North America, where **two types** are recognised, one confined to the river-valleys of the Western States, the other found in the marshy country on the Eastern seaboard. Both varieties have a definite seasonal incidence—in the late summer and early autumn—suggesting transmission by mosquitoes, probably, it is thought, *Culex tarsalis* and perhaps *Aëdes ægypti*, in which insects there is a latent non-infective or incubation period of four or five days after which it remains infective for life. In the horse, and in laboratory-animals and in man, there are **two phases** of the infection : (1) a pyrexial period of a few days during which the virus is present **in the blood** and multiplies in the viscera : and (2) excretion of the virus on to the nasopharyngeal mucosa and its passage centripetally **to the central nervous system.** Infants and young children are most liable to infection, the disease in them being usually fatal, whilst in adults its incidence is less frequent, it runs a more prolonged course, and often ends in recovery.

An analogous disease known as " **taiga** " or " **spring-summer encephalitis** " [2] is endemic in wooded localities in Siberia and probably in some districts of European Russia. It affects wood-cutters and hunters ; is carried by ticks ; and is characterised by sudden onset with fever, vomiting, meningismus, loss of consciousness, and paresis and paralysis and wasting of muscles, especially of the upper limbs and neck. The virus has been isolated from the brain in fatal cases in man, and also in rodents (squirrels and hares) living in the endemic areas. It has analogies, but is not identical, with the viruses of the St. Louis and the Japanese B varieties of encephalitis.

RABIES or **HYDROPHOBIA.** This is an infective disease which occurs especially in carnivora and which can be transmitted to other animals and to man by the bite of an infected animal, usually a dog or cat. The virus is found in the saliva, and seems to have an affinity for the salivary glands. It is very minute and filtrable, but has not yet been cultivated outside the living animal body.

In the majority of cases, the virus gains entrance by the infected wound and passes by way of the nerves to the spinal cord and brain. As stated, it also accumulates in the salivary glands.

In man, the incubation period varies from three weeks to twelve months, but is usually from four to six or eight weeks, with an average of forty days, subsequent to the bite. The premonitory symptoms are pain at the site of injury and along the nerves leading from it. Later, there is increased irritability with exaggerated reflexes, spasms, especially in the muscles of deglutition, and, still later, great weakness, paralysis, coma and death.

On examining the brain with the **naked eye,** a few hæmorrhages may be present in the medulla, but no characteristic pathological changes have been described. **On microscopical examination,** accumulations of lymphocytes and plasma-cells are seen in the perivascular spaces of the nerve-centres, and also various degenerative and necrotic changes in nerve-cells, no one of these phenomena, however, being confined exclusively to this disease. They may all be found in other forms of encephalomyelitis. In some cases of rabies, these inflammatory or encephalitic changes are inconspicuous, but in the majority they are present if search be made for them and are usually most intense in the substantia nigra, red nucleus, and the grey matter of the pons and medulla, as well as in that of the spinal cord. In the affected areas, the

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[1] " Virus Diseases acquired from Animals," by S. P. Bedson, London, *Lancet,* 1940, ii, 577. *See also* " St. Louis Encephalitis and Equine Encephalomyelitis," Annotation, *Lancet,* 1942, i, 51.

[2] M. P. Chumakov and S. G. Gladkikh, *Bull. Biol. med. exper. U.S.S.R.,* 1940, 7, 2 (quoted in editorial on " Two New Virus Diseases of Man " in *Lancet,* 1940, ii, 657).

degenerated cells and tissue-debris are removed by phagocytic microglial cells which often become aggregated into little groups which have been described as "rabies tubercles." In the cord, the lesions are generally most definite in the segmental areas corresponding to the peripheral nerves from the site of the infected wound. The most characteristic change is the presence of the **Negri-bodies** in the nerve-cells (Fig. 60). These inclusion-bodies vary in shape, but are usually rounded or ovoid, measuring 3 to 10 μ in diameter, but may reach 25 μ, and are found in the cytoplasm of the cell or in one of the dendritic processes. They may occur in the nerve-cells in any part of the brain, but are most abundant in those of the hippocampus major or in the Purkinje-cells of the cerebellum. Opinions differ as to their nature, but it seems reasonable to regard them as micro-colonies of virus. When stained by Giemsa's method, the homogeneous ground-substance of the Negri-body shows a light blue coloration, and in it there are larger pink areas and smaller rods or granules, reddish-pink in colour. In some cases in which Negri-bodies are not found, the nerve-cells show masses of small granules in their cytoplasm. The disease is transmissible to rabbits by subdural, intracerebral or intravenous inoculation of an emulsion of infected brain- or cord-tissue, or virus from salivary glands. The virus may remain viable, even in decomposing and decomposed brain-tissue, for as long as two months or more. If vaccine-treatment is carried out in the early stages of the incubation-period of the disease, the development of the characteristic symptoms does not take place. Pasteur treated infected patients by injecting subcutaneously a vaccine prepared from the spinal cords of rabbits which had been experimentally inoculated with the virus. These cords were dried in air over caustic potash for

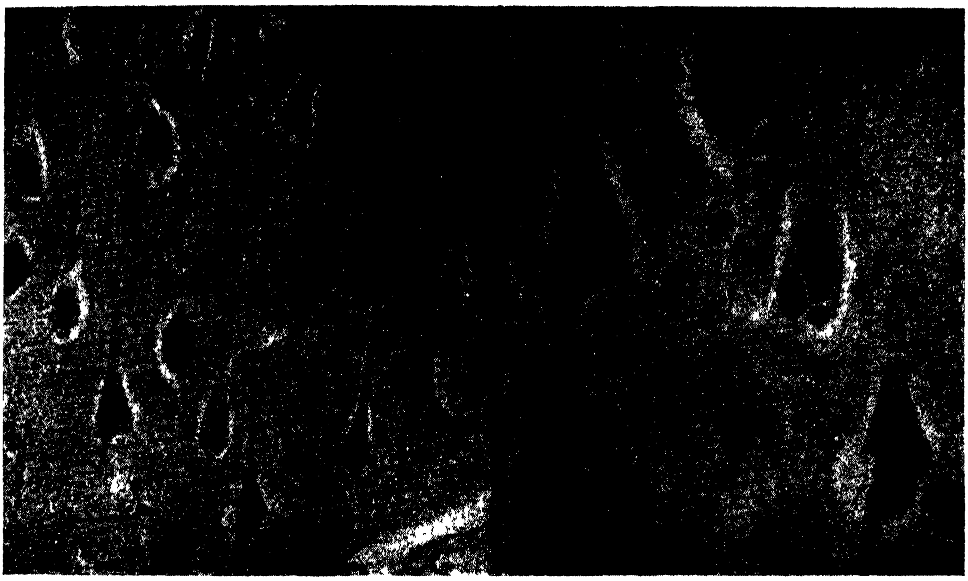

FIG. 60. *Rabies*, showing ovoid "Negri-bodies" with darkly-stained granules in the nerve-cells from the brain of a monkey. (By courtesy of Dr. Campbell.) Mann's methyl-blue and eosin.

varying periods of from one to sixteen days, and their suspensions exhibited different stages in a decreasing virulence—those dried for the longer period being non-virulent. The first injections given were from the non-virulent and the final from the virulent suspensions. Other methods, such as injection of virus attenuated by heat or by chemicals, or of very dilute suspensions of a virulent virus, have been used with success. Full details of the methods will be found in bacteriological text-books. During specific immunisation against the disease, some cases are recorded in which paresis or even a rapid paraplegia of the legs has occurred, and occasionally a condition resembling Landry's paralysis (pp. 108 and 1051–2) was produced.

ACUTE ASCENDING MYELITIS. Hurst and Pawan (1931) reported outbreaks of rabies amongst the inhabitants of Trinidad, the victims being mostly children under fifteen years of age, in which the transmission was by the bite of a vampire-bat which was found to be infected with rabies. This disease is prevalent among cattle, horses and mules in South America, and the vampire-bats which are numerous in Trinidad (off the coast of Venezuela) feed on blood and become carriers of infection. Negri-bodies are found in the hippocampus-area in the brains of infected bats, and the disease can be transmitted from them to rabbits by intracerebral inoculation. The main feature of the disease in this outbreak was an **ascending myelitis.** The earliest manifestation was paræsthesia, and this was followed by paresis and paralysis, commencing in the toes or feet and in a few cases in the arms—the level of localisation in the cord probably being dependent on the site of infection. A similar condition was described by R. E. Knutti (1929) and the diagnosis was based on the presence of Negri-bodies in the nerve-cells in the ventral horns of the spinal cord. Sabin and Wright [1] (1934) recorded a human case of ascending myelitis associated with visceral necrosis, following the bite of an " apparently normal " *Macacus rhesus* monkey. In this case the virus was present in the brain, spinal cord and spleen, and on inoculation into rabbits the neurotropic character of the virus was established. They also recorded that intravenous inoculation of the virus from the human case into monkeys produced a generalised disease resembling vaccinia, with a rash on the face, buccal mucous membrane and conjunctiva. Primary myelitis occurring in rabbits inoculated with herpes-virus has also been recorded.

ACUTE LYMPHOCYTIC CHORIOMENINGITIS. This disease is described on p. 1000 under Diseases of the Nervous System. The main features are an acute onset with development of symptoms of meningeal irritation. A virus has been isolated and cultivated on the chorio-allantoic membrane of the developing chick-embryo. A condition similar to that occurring in the disease in the human subject has been produced by inoculation of the virus into monkeys, guineapigs and mice ; and the accidental infection of laboratory-workers with the virus under investigation has occurred (pp. 1000–1). It is highly probable, as suggested on p. 1000, that we are dealing with **a group of closely allied diseases,** in the production of which more than one variety of virus is concerned.

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[1] A. B. Sabin and A. M. Wright, *Jour. Exper. Med.*, 1934, **59**, 115, and A. B. Sabin " Studies on the B Virus. III : The Experimental Disease in *Macacus rhesus* Monkeys." *Brit. Jour. of Exper. Pathol.*, 1934, **15**, 321. They believe that previous attempts to establish this virus in *Rhesus* monkeys had failed because " the majority of them were immune, probably as a result of natural infection, and that the human disease from which the B virus was isolated was caused by the bite of a monkey which was infected with it."

GROUP III

(General: often predominantly Catarrhal)

EPIDEMIC or INFECTIVE PAROTITIS (Mumps). In this disease the most obvious lesions are a non-suppurative enlargement of one or both parotid glands (p. 711) and not infrequently of the submaxillary and sublingual glands and sometimes of the testicle (p. 907), the ovary (p. 927), the mamma and occasionally the pancreas. The infected parotid glands are inflamed, the inflammation being of acute interstitial type, followed by various stages of degeneration of the acinus-cells, whilst the cells of the ducts show no important changes. The degenerated cells are swollen, the cytoplasm is granular and the nuclei hyperchromatic. Infiltration of the glandular tissue with lymphocytes and plasma-cells occurs, but there is no invasion of the tissues with polymorphonuclear leucocytes. Œdema of the stroma is a characteristic feature and small hæmorrhages may be present. No cytoplasmic or intranuclear inclusions have been found. In the infected testicle, according to Stengel (1936), yellowish turbid fluid may be present in the tunica vaginalis—the organ is firm and elastic and shows numerous punctate hæmorrhages. The intertubular connective-tissue of the testicle is œdematous, and the pathological infiltration is largely of "neutrophil and endothelial phagocytes." Atrophy of the tubules with or without interstitial fibrosis has been described. An **involvement of the nervous system**, suggesting that the causal virus is distinctly **neurotropic,** is common and may be present in as many as 30 or even 40 per cent. of cases in some epidemics, in which such nervous manifestations are more frequent than amongst an equivalent number of sporadic cases. The occurrence of meningitis (p. 979), meningo-encephalitis, encephalitis, encephalomyelitis, and less frequently labyrinthitis (deafness is a not uncommon sequel of mumps) and occasionally involvement of the eye, has suggested to some recent writers that the infection is primary in the central nervous system, and that the involvement of the parotid and other salivary glands is a secondary phenomenon, as the parotid swelling may not supervene until perhaps the sixth or seventh day of the illness in which the nervous symptoms have already manifested themselves.

The histological changes in the nervous system in the rarely occurring fatal cases closely resemble in character those already described for various other viral infections; and in the living patient the phenomena in the **cerebrospinal fluid** are also similar—a pleocytosis of from 50 or 100 up to as many as 2,000 or 3,000 cells per c.mm., of which some 90 to 95 per cent. are usually small lymphocytes, though in exceptional cases polymorphs may predominate in the early stages. It is stated that the fluid in practically all cases of mumps shows this definite **mononuclear pleocytosis** even when no neurological symptoms are manifest. Protein is usually normal or but slightly increased, and sugar and chlorides are unaffected. The colloidal-gold curve may be normal or exhibit a slight mid-zone rise. In the **blood**, although the total leucocyte-count may demonstrate a leucopenia, there is usually a lymphocytosis, both relative and absolute.

If filtrates of the saliva or of suspensions of the infected glands, obtained in the early stages of the disease from the human subject, are injected into the parotid (Stenson's) duct or into the testicle of monkeys, a parotitis or an orchitis is produced, and the histological picture in each experiment is similar to that seen in the spontaneously infected parotid gland or testis. The saliva becomes non-virulent between the sixth and ninth day of the disease. Johnson and Goodpasture (1935) were able to transmit the disease back to human volunteers by means of the virus from infected monkeys. Intracerebral inoculation in monkeys results in degenerative changes in nerve-cells of the brain and cord, and meningitis may be associated with these changes.

RUBEOLA or Measles. Hektoen (1905) demonstrated that this disease could be produced artificially in man by subcutaneous inoculation of the blood of a patient, if it was taken immediately after the appearance of the rash. The typical clinical picture—temperature, rash, etc.—is obtained when the infected blood or filtered nasal or pharyngeal washings from the patient are inoculated into monkeys (*Macacus rhesus*), or when the virus from rabbits which have had repeated injections is transferred to susceptible children. The blood ceases to be infective in from thirty to sixty hours after the appearance of the rash. Various strains of virus from the blood and filtered naso-pharyngeal washings of measles patients have been identified. Elementary-bodies have been obtained in smears from the infected cornea of rabbits. Plotz (1938) reports that he has succeeded in growing the virus in a special medium containing minced chick-embryo in Tyrode's solution and monkey-serum. With the tenth subculture, he injected a *rhesus* monkey subcutaneously; the animal appeared ill ten days after the injection and an extensive maculo-papular rash appeared and lasted for three days. It has been shown that the serum from a convalescent patient or from adults who have presumably had the disease in youth is capable of neutralising the action of the virus, and such serum has been used with promising results in both prevention and treatment, as has also "immune-globulin," a concentrated preparation of human placental blood and tissue.

Pathological Lesions. The skin-rash shows a small round-celled infiltration about the blood-vessels and sweat-glands; and, in the deeper layers of the epidermis, areas of necrosis may be found. In the mucous membrane of the mouth and upper respiratory passages, catarrhal inflammation is often very prominent. The lymph-follicles may be swollen or even ulcerated; and the lungs nearly always show bronchopneumonia. **Meningitis** and **encephalomyelitis**, diffuse or occasionally focal in distribution, sometimes occur, and the results of these may be evanescent or lasting, and of all degrees of severity, the symptoms depending upon the distribution of the lesions in the cerebrum, cerebellum or spinal cord. Though the actual case-mortality is low in the earlier stages, the later results in some cases may be serious, *e.g.*, spastic paraplegia, cerebellar ataxia, and occasionally sleep-irregularities, alteration of disposition and other mental changes, *i.e.*, symptoms dependent upon lesions similar or analogous to those already described as occurring in other forms of viral encephalitis (p. 110 *et seq.*). The **cerebrospinal fluid** usually shows a moderate lymphocytic pleocytosis and slight protein-increase; and in the blood, after a transient slight leucocytosis, there is typically a neutrophil leucopenia, sometimes considerable in degree.

The **Koplik's spots,** regarded as pathognomonic of measles, are small areas of thickened epithelium in the mouth—this epithelium has undergone fatty degeneration and exhibits a pale, almost milky-white centre surrounded by a deep-reddish periphery. They are situated on the buccal aspect of the cheeks and lips or on the gums and palate. It is difficult to decide whether certain of the various pathological lesions are due to the action of the virus or to secondary bacterial infection. It seems probable that the cutaneous reaction, the neurological lesions, the early conjunctivitis and even the alimentary and respiratory catarrh are originated by the virus; but the catarrhal conditions may be and frequently are intensified by the secondary bacterial infection. Though the lymph-nodes are not swollen to any great extent, a lymphoid hyperplasia of the faucial tonsils and pharyngeal lymphoid tissue has been described, and in the centres of these swollen follicles multinucleated giant-cells are present. It is claimed that the presence of these cells is pathognomonic of measles, and that the detection of them in an excised follicle enables a diagnosis of the disease to be made from twenty-four to ninety-six hours before the appearance of Koplik's spots or the cutaneous exanthem.

RUBELLA or German Measles. The pathological changes in this disease are analogous to, but usually milder than, those described above for measles, and are probably produced by a virus. A generalised enlargement of the lymph-nodes, including the occipital group, the macular rash and the absence of Koplik's spots, serve to differentiate this infection from that of measles.

PSITTACOSIS[1] **or Ornithosis.** This disease is not uncommon in parrots, parakeets and budgerigars (love-birds), and has been found also in canaries and finches ; it is transmissible to and by pigeons ; and a similar and probably identical disease, cummunicable to man, has been identified as infecting the fulmar petrel, the young of which are used for food in the Faroe Islands and Iceland.[2] In these birds, the infection is characterised by the occurrence of diarrhœa, wasting, and frequently by inflammatory changes in the duodenum, but usually with no evidence of pneumonia. Multiple necrotic areas are found in the liver, and there may be catarrhal conditions of the lungs, and pericardial and peritoneal effusions. Bird-carriers, showing no obvious symptoms of the disease, are now known to occur. The infective agent is rather larger than the majority of viruses, but is filtrable and is present in the blood, the internal organs, mucous discharge from the respiratory tract and in the fæces. Intracerebral injection in monkeys, rabbits and guineapigs produces degeneration of nerve-cells and meningitis. Intranasal or intratracheal inoculation gives rise in monkeys to a pneumonic condition similar to that seen in man. The infectivity from parrot to man is very high ; the infection seems to take place by inhalation, probably in dust from infected feathers, and the principal features in human cases are inflammation of the mucosa of the upper respiratory tract, a patchy type of pneumonia and general symptoms resembling those of typhoid fever. In the lung, the irregular patches of consolidation are widespread and simulate in their distribution and character the type of pneumonia also seen in influenza. The alveoli contain a small amount of fibrinous exudate and some hæmorrhage, but in the exudate there is a comparative absence of polymorphonuclear cells—the cells present being almost entirely mononuclears. These cells are probably derived from the cells of the reticulo-endothelial system, though some authors maintain that they are proliferated cells from the lining endothelium of the alveoli. Congestion and œdema of the brain and spinal cord have been described. Bedson and his co-workers (1930, 1932, 1934, 1936) demonstrated in the tissues the presence of very minute pleomorphous and usually rounded bodies arranged singly or in pairs. These can be stained by Giemsa's method; and, in the blood, can be thrown down by high-speed centrifugalisation and grown in tissue-culture. They are agglutinated specifically by psittacosis anti-serum. On these grounds, it is suggested that they are particles of a causal virus. They are rather larger than most of the particles of other viruses which cause disease in human subjects. Complement-fixation tests are valuable for the diagnosis of psittacosis, both in birds and in man.

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[1] From Greek ψιττᾰκός, *psittakos*, a parrot.

[2] S. P. Bedson, *loc. cit.*, p. 578.

EPIDEMIC INFLUENZA. The claim, now discredited, that Pfeiffer's bacillus was the cause of influenza was put forward by many observers, and was based largely on its presence in the naso-pharynx and in the upper respiratory passages in a considerable proportion of cases of the disease. There is, however, a complete lack of experimental evidence to support this view, and in some epidemics of the disease this bacillus has been absent. The sudden onset, the rapid epidemic spread of the infection and the highly infectious character of the disease naturally suggested the probability of **a virus** as the cause. Though several observers had claimed to have isolated a specific virus, it was to the work of Laidlaw, Andrewes and Smith in the National Institute for Medical Research, London (1933), that we owe any real advance in our knowledge of the ætiology of this disease. During the epidemic of 1933, they were able to infect ferrets by intranasal instillation of the filtered washings from the nasopharynx of early cases of typical influenza. The ferrets developed pyrexia, sneezing, watery discharge from the nose and eyes, lethargy and muscular weakness; and it is on record that one of the research-workers at the National Institute contracted a typical attack of influenza after an infected ferret, which he had picked up, had " sneezed in his face." Shope (1931, 1932, 1934) isolated a virus from swine-influenza, a disease which was first recognised in the United States in 1918, and by intranasal instillation in ferrets produced the symptoms characteristic of the disease—symptoms which are indistinguishable from those occurring in ferrets after intranasal instillation of the human influenza-virus. Later, Shope (1935), and Francis and Shope (1936), confirmed and extended the observations of Laidlaw and his co-workers. On **histological examination,** the mucous membrane of the nose in infected ferrets showed acute inflammation, with disappearance of the ciliated cells.

The serum from a number of persons with no history of any recent attack of influenza was found to contain antibodies which had a neutralising effect on the virus, and the serum of convalescent human cases of influenza as well as that of ferrets which had recovered from experimental inoculation was found to have developed a more pronounced capacity of neutralisation. The presence of these antibodies in the blood of apparently healthy individuals makes it difficult to prove by serological tests that experimental inoculation of this virus into the human subject will produce influenza. Although an increased titre in a serological reaction on the part of the patient is not of itself sufficient evidence, as such increase has been found to result from the introduction of a non-specific antigen, *e.g.*, an increased typhoid agglutination may follow a non-typhoid febrile illness, the evidence in favour of the causal relationship of the virus to influenza is now practically conclusive.

It has also been suggested by some veterinary writers that there may be some connection between influenza in the human subject and canine distemper, and they believe that these two diseases may be produced by viruses which, if not actually identical, are at all events closely allied serologically ; and, in America, considerable success appears to have attended the use of a mixed vaccine prepared by the inoculation of fertilised hen's eggs containing living chick-embryos simultaneously with the viruses of both influenza and distemper—a combined vaccine so prepared having been found to be more efficacious than one made from the influenza-virus alone[1]. In December, 1940, half-a-million doses of this mixed vaccine were sent from America to Britain, but the ship carrying them was sunk at sea. It is probable that there are several closely-allied strains of influenzal virus.

As in a number of other viral infections, involvement of the nervous system is a common accompaniment or sequel of epidemic influenza ; and certain cases of acute disseminated encephalitis and encephalomyelitis following upon influenza-like pyrexial attacks have been described as "post-influenzal." In the comparatively few fatal cases of this nature as yet investigated, one of the most characteristic phenomena is **perivascular demyelination** of the sheaths of the nerve-fibres immediately around the vessels in the affected brain and cord. Small outbreaks of **encephalitis** and **polyneuritis** coinciding with epidemics of true influenza are now on record, but complete proof that the influenzal virus is causal in such cases is still lacking.

In this connection it must be emphasised that many cases of meningitis caused by Pfeiffer's bacillus and other members of the *Hæmophilus* bacillary group have, in the past, been recorded under what is now recognised as the misleading title of "influenzal" meningitis. A meningitis caused by these organisms is a purulent and, if untreated, almost always fatal condition which, if we grant (as we now seem bound to do) that influenza is a virus-produced disease, has no relation to true influenza other than one of coincidence. By the experimental infection of a considerable number of volunteers by the inhalation of living and virulent cultures of Pfeiffer's bacillus (now regarded as being mis-named *Bacillus* or *Hæmophilus* "*influenzæ*"), a number of Russian bacteriologists (*Lancet*, 1936, *ii*, 1381) produced a febrile reaction coming on within a few hours and characterised by catarrh of the upper respiratory passages, severe headache, pains in the joints, and, in some instances, labial herpes. This artificially-produced illness was however, uniformly more transitory (lasting only one or two, or at most four or five, days) and less severe in its nature and sequelæ than genuine epidemic influenza ; and, moreover, in the **blood** of many of these patients a **leucocytosis** chiefly polymorphonuclear, of 12,000 or 15,000 was produced, although in milder cases it might not exceed 11,000 per c.mm., a result in marked contrast with the **leucopenia** typical of true epidemic influenza.

For a note on so-called "**Viral Pneumonia**" or "**Viral Pneumonitis,**" see p. 538.

CORYZA[2] or **Common Cold** (p. 502). It is generally agreed that the "common cold" is due to a viral infection, and its transmission to anthropoid apes and to human volunteers by the intranasal instillation of filtered washings from the nasopharynx of patients with the disease has been claimed by various writers, though it is, of course, difficult in such experiments to eliminate the risk of natural or spontaneous infection. The catarrhal symptoms and lesions caused by the virus are intensified by the action of various organisms of secondary infection such as the pyogenic cocci or Pfeiffer's bacillus, but, on the evidence available, these organisms cannot be regarded as the primary infective agents.

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[1] Whilst experimenting on the inoculation of chick-embryos with the influenza-virus (of which two types, A and B, are now generally recognised), G. K. Hirst, at the Rockefeller Foundation's Laboratories, New York, finds that the red corpuscles of the fowl are specifically agglutinated by the allantoic fluid of the chick-embryos infected with either type of the virus. (*Science*, 1941, **94**, 22.)

[2] "*Coryza*": *see* footnote on p. 41.

YELLOW FEVER or Jungle Yellow Fever. This infection in man appears to be merely an " incident," as it were, in the main life-story of the virus—yellow fever being primarily an infection of animals. Recent investigations have proved that this disease is more widespread than was at one time supposed. It is endemic in the West Indies, Northern and Central parts of South America and in Sierra Leone and adjacent regions of West Africa and in the Sudan. It has been proved by Reed, Carroll and others that man is infected by the bite of a mosquito, *Aëdes ægypti* or *Stegomyia fasciata* (*S. calopus*), or one of several other species, and it has been shown that the mosquito is not infective till from nine days to three or four weeks after it has bitten a yellow-fever patient, though the virus is present in its body from the time the bite took place ; in fact, only a mosquito which has ingested blood during the first three days of the illness in the human subject can transmit the infection, the virus having disappeared from the blood of the patient or become non-virulent after that period of time. Accidental infection in human subjects, who were examining blood which they had withdrawn from infected patients, has been recorded. The virus is filtrable, its particles measuring 17 to 28 $\mu\mu$, and it has been proved to be present in the salivary secretion of the mosquito.

Monkeys and perhaps certain other kinds of wild animals are now believed to be the reservoir of the disease in such places as Trinidad, the Amazon Valley and the West-Central Hinterland of Africa. These wild animals need not necessarily suffer from the active disease, but act as carriers ; and amongst them the virus is spread probably by some other transmitting agent, not the usual house-haunting yellow-fever *Aëdes* mosquito, but some other kind, which does not live in houses, but in the open. The disease may, perhaps, also be carried by ticks (p. 431).

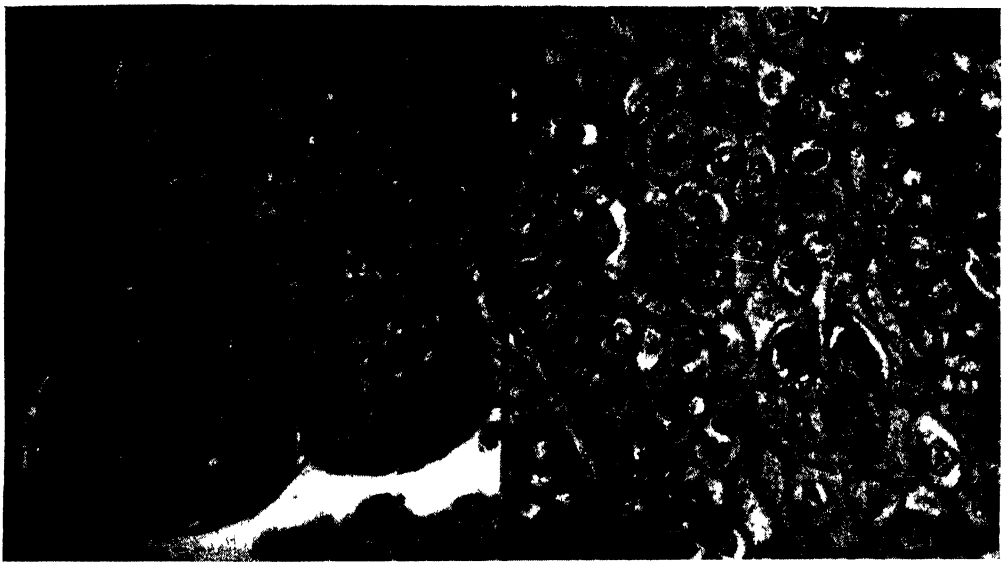
The *Macacus rhesus* monkey is highly susceptible, and can be infected by subcutaneous or intraperitoneal injection or even by smearing the virus on the undamaged skin. The disease in the monkey produces results similar to those seen in the human subject. After an incubation-period of three or four days, a considerable degree of pyrexia supervenes, with jaundice, albuminuria, casts in the urine, bleeding from the gums and sometimes from the stomach (black vomit), and a leucopenia in the blood. Infectivity can be maintained experimentally by passage from animal to animal by inoculation with blood or with emulsion of liver. By repeated brain-passage in mice, the virus can be converted into a neurotropic form, which may cause encephalitis when injected intracerebrally, and which may in turn be reconverted into the viscerotropic virus by its direct injection into the liver of monkeys.

Post-mortem Appearances in Man. The stomach shows acute gastritis and contains dark altered blood. The intestines may be congested and occasionally ulcerated. The mesenteric lymph-nodes are enlarged. In the liver, hyaline necrosis is present, especially in the mid-zone of the lobules, and the cells which have escaped necrosis are fatty. The kidneys show acute glomerulonephritis, along with fatty and necrotic changes in the cells of the tubules. Congestion of, and hæmorrhages into, the meninges are sometimes present, and petechial or larger hæmorrhages occur in the pericardium and peritoneum.

The serum of convalescent patients contains antiviral immune-bodies, the specific nature of which can be demonstrated by the mouse-protection test of Sawyer and Lloyd (1931). In this test, a mixture of the virus and the patient's serum to be tested is inoculated intraperitoneally into mice, and at the same time an injection of starch-solution is made into the brain of the mouse. If the serum contains no specific antibodies, the animal will die of encephalitis. This test is very valuable for estimating immunity, since the presence of the antibodies can be demonstrated by it several years after infection.

GROUP IV
(Tumour-producing)

The "Rous-sarcoma of fowls" and allied virus-produced tumours are dealt with in the chapter on Tumours (p. 288). The experimental production of **leukæmia** and **erythroleukæmia** (pp. 625 and 638) and of **various types of sarcoma** by the inoculation of fowls with a filtrable virus is described by Engelbreth-Holm[1] of Copenhagen (1942). For **Hodgkin's disease** (lymphadenoma), which some authors, admittedly with as yet little positive evidence, regard as a viral disease, *see* pp. 676 and 695. The "**Shope skin-papilloma**" of the rabbit's ear is mentioned on p. 287.



(A) × 230. (B) × 300.

FIG. 61. *Molluscum contagiosum*: section of the skin showing the inclusion-bodies in the cells (dark granules). Kull's stain.

Molluscum Contagiosum is a contagious disease of the skin characterised by the presence of small red nodules, warty in appearance, which undergo necrosis and form ulcers which discharge a caseous material. In the epithelial cells of the lesions, large **acid-staining ("oxyphil") inclusion-bodies** are found, and, in these so-called **molluscum-bodies,** minute granules are seen. These granules represent the virus which is filtrable and capable of producing the disease on experimental inoculation. The molluscum-bodies have been regarded as the result of the reaction of the cell to the virus, but they have been separated from the cell by micro-dissection by Van Rooyen (1938), who considers them as part of the infective agent. In the **common cutaneous wart,** the presence of a filtrable virus has been demonstrated by Findlay and others (*see* also p. 330).

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[1] "Spontaneous and Experimental Leukæmia in Animals," by Julius Engelbreth-Holm. Oliver & Boyd, Edinburgh, 1942.

CHAPTER V

BACTERIAL INFECTION AND IMMUNITY

BACTERIAL INFECTION

Bacteria, having entered the tissues of the host, may multiply, cause local irritation at the site of invasion,[1] spread more or less widely from that spot, enter the blood or lymph-stream and be distributed throughout the body, or be arrested in lymph-nodes. With certain pathogenic microbes, however, there is no general invasion of the tissues ; the multiplication takes place only at or near the site of entry, and the harmful effects are, in the main, due to the products of their growth which are absorbed and distributed by blood and lymph. Thus a serious illness or a fatal result may ensue either in cases in which wide dissemination of the bacteria takes place, or in those in which the organisms remain localised.

Although the infecting microbes may enter through the unbroken skin or mucous membrane, they do so more readily if these covering and protective structures are damaged or their continuity broken by abrasions, insect-bites or wounds ; and the invading micro-organisms are more likely to spread from the site of entry if from that situation there is good lymphatic drainage —as, for example, the nasal mucous membrane, the tonsils or the intestines. They may become lodged in the crypts of the tonsils, or in the mucous glands : multiply locally : and then reach the subepithelial tissues and give rise to a general invasion. The main methods of infection are : (1) direct contact of the bacteria with the skin or mucous membrane : (2) inhalation of air contaminated with bacteria, as by the " droplet-method " from infected patients or from dust containing dried-up sputum or fæces : (3) ingestion of food, drink, or other material, *e.g.*, the dust of workshops, containing bacteria or contaminated with them by flies.

The presence of bacteria in the blood is, in some cases, merely a passing phase or stage in the development of the infection. Thus, in typhoid fever, the bacteria can be obtained from the blood by culture during the first week of the infection,[2] but later they become localised in the lesions in the intestine, spleen, etc. Even in cases in which the bacteria are present continuously in the blood, *e.g.*, in fatal septicæmias, it has been suggested that this constant presence is, in the majority of instances, due merely to an overflow from the site of infection—and that active multiplication does not, as a rule, take place in the blood-stream.

Conditions Favourable to Infection. Two main factors are concerned—the susceptibility of the individual, and the virulence of the organisms. The numbers of the invading organisms and the avenue of entrance also play some part. Conditions such as fatigue, cold, trauma, specific fevers, starvation and deficiency of vitamins A and C favour infection by lowering the vitality of the host. But the wide variation of susceptibility which exists among healthy individuals cannot be due merely to a lowering of vitality by such causes.

The virulence and aggressiveness (or power to invade) of micro-organisms vary greatly, and it may be said that, as a general rule, organisms which invade rapidly and widely produce more serious toxic effects than those which tend to remain localised. There are, however, notable exceptions. The bacillus of diphtheria, the bacillus of tetanus, and the vibrio of cholera, multiply at the site of infection, and do not invade the whole body ; but each can produce serious toxæmia. The virulence of an organism is often raised by passage through a series of susceptible individuals. This explains why cases occurring near the beginning of an epidemic are frequently mild in comparison with those seen later. On the other hand, the virulence may be lessened by passage through less susceptible animals or by the growth of the micro-organism in unfavourable conditions as regards food, temperature and moisture.

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[1] *See* Chapter II on " Inflammation," p. 15 *et seq.*

[2] For their culture from the bone-marrow see p. 606.

The invasion by infective organisms and the spread in the tissues of the host are determined by the place of entry, the nature of the tissue at the site of entry, the direction and completeness of the lymphatic flow, and the type of causal organism. Thus the majority of the pyogenic affections of the skin are caused by staphylococci. These may be normal inhabitants of this tissue which become pathogenic, producing pustules, boils and carbuncles only when they gain access to the underlying tissue through mechanical injuries, such as the pulling out of a hair, or by a scratch. Streptococcal infection, commencing in the same way, may produce widespread erythema, cellulitis or localised abscesses. Again, in the nasal cavities, in the nasopharynx, on the surface and in the crypts of the tonsils, and in the mouths of apparently healthy people, various types of potentially pathogenic bacteria such as pneumococci, hæmolytic streptococci, meningococci, and diphtheria bacilli, are often found. These may not produce any lesions in the host, but such " carriers " are capable of passing on the infection to others by coughing or sneezing ; or, if their own general health be lowered or their tissues damaged, the carriers may themselves be attacked by the micro-organisms which they " carry." Under certain conditions, the organisms invade the tissues of the host, reach the lungs, brain or other organs or tissues, and give rise to pneumonia, meningitis, or diphtheria. The flora of the intestine may contain analogous potentially pathogenic bacteria, and these, either alone or in association with other organisms, are capable of producing serious pathological lesions. Certain types of the *same group* of organisms often have a definitely selective action for certain tissues, *e.g.*, the so-called " *Streptococcus viridans* ' for the valves of the heart (p. 455), other varieties of streptococci for the throat or for the gall-bladder, and others for the uterus. The bacillus of typhoid fever and the vibrio of cholera produce their lesions when they reach tho alimentary tract ; the bacillus of tetanus and the clostridium of Welch are most active if they are developing in necrosed or damaged tissues ; and the bacillus of tuberculosis finds its most ready entry through the lining-membranes of the respiratory passages (p. 553) and the intestine (pp. 71 and 755) ; along with which, in the case of the tubercle bacillus, may be included the lymphoid tissue of the tonsils and naso-pharynx—and also the various lymphatics draining these structures into the cervical, bronchial and mesenteric lymph-nodes respectively.

Various explanations have been advanced as to why different bacteria and different strains of the same organism attack at different points, multiply in such different environmental conditions, react in such different ways, and produce such different lesions, but no useful purpose will be served by discussing these problems here. Their real explanation and significance are not yet fully understood. Perhaps a more intensive and thorough study of the chemical reactions of bacteria and of the tissues may help to solve the problem.

Products of Bacterial Growth. It has been stated that bacteria do not necessarily multiply in the blood-stream, and that their presence there or in the tissues does not in itself necessarily constitute disease. Their pathogenic action is due to the chemical products resulting from their interaction with the tissues of the body, or with various protein and carbohydrate substances found in these tissues. Some bacteria, *e.g.*, the bacillus of diphtheria and the bacillus of tetanus, grown in media containing proteins and/or carbohydrates, give rise to highly poisonous substances which can be separated from the bacteria by filtration, and are capable of producing in animals lesions similar to those caused by infection with the living organisms. These substances have been grouped as bacterial toxins (**exotoxins**), but it should be clearly understood that no worker has yet succeeded in isolating from these products of bacterial growth a " toxin " in a chemically pure state. With other bacteria, the filtrates are either non-toxic or only feebly toxic, and in these it would appear that the toxic substances are more closely bound to the bacterial cells, and are liberated only when the bacterial cell itself is broken up either in the tissues of the host, or by autolysis outside the body, or by mechanical destruction. These are the so-called **endotoxins** or "autolysates," which, therefore, may be regarded as substances of a toxic nature which exist in the bodies of certain bacteria and which can be liberated only by actual breaking up of the bacterium : the exotoxins, on the other hand, appear in actively-growing fluid cultures of a comparatively few types of bacteria and are elaborated apparently during the growth-period either as metabolic products from the bacterial bodies themselves or by their interactions with certain chemical substances, *e.g.*, carbohydrates, proteins, etc., in the media in which the growth is taking place.

Results of the Action of these Toxins. These may be classed under three types of reaction—the cellular, the serological, and the allergic. It is true that this separation is artificial, as both the serological and the allergic results are due to cellular response, and all three reactions are interlocked and closely associated, but this classification is suggested for convenience of description.

1. **Cellular Response.** There may be a definite leucocytic response, both in the form of an increased production of white cells by the blood-forming tissues (p. 603 *et seq.*), and by the stimulation of the individual phagocytic and other activities of the leucocytes themselves by the micro-organisms or their products acting as "**stimulins**" (Almroth Wright[1]). Another point of interest noted by Wright in his address (*see* footnote) is that vaccines act, not merely—as was formerly supposed—by stimulating certain of the tissues, *e.g.*, of the reticulo-endothelial system, to produce opsonins (p. 133) and other anti-bacterial bodies which then pass into and are found in the plasma, but they also function as direct **leucocytic stimulins** (a *rôle* which, it is believed, is also played by sulphapyridine and other similar drugs—*see* footnote, p. 985—now used in the chemotherapy of various infective conditions). On the other hand, if the bacterial poisons are highly virulent, this response may be inhibited, and the main damage fall on the blood-vessels, with resulting inflammatory œdema, as is seen in very acute cases of influenza during epidemics. The toxic substances

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[1] "The Need for Abandoning Much in Immunology which has been Accepted as True," an Address by Sir Almroth Wright to the Royal Society of Medicine, Dec. 12th, 1941 (*Brit. Med. Jour.*, 1942, **i**, 50).

are absorbed and carried in the blood-stream to various parts of the body, and are capable of producing degenerative changes such as cloudy swelling, fatty degeneration, amyloid and hyaline degeneration and necrosis, in the various organs and tissues. These changes are most evident in the more highly functioning cells, for example of the liver and kidney, which are concerned largely with the absorption and excretion of the poisons. The damage to the blood-vessels, especially the capillaries, may lead to hæmorrhage, *e.g.*, the petechial hæmorrhages so often seen in or under the skin or in the various organs or tissues in infective disease as a result of this vascular degeneration. In some cases, the degenerative changes may be almost wholly in the cells of the nervous system. The most characteristic type of such degenerative change is seen in botulism, in which the toxin produced in the infected tinned meat, etc. (*i.e.*, *outside* the living body), acts within a few hours after ingestion, producing serious nervous manifestations and death from damage to nerve-centres. There is no evidence that the organism invades the tissues or multiplies in them. In tetanus, the organism multiplies in the tissues, but remains localised, and the products of growth are absorbed and act mainly on the cells of the central nervous system, reaching them from the site of the lesion by way of the motor nerve-sheaths or by the blood-stream.

2. **Serological Response.** The exotoxins, when introduced into the tissues, lead to the production of antitoxins; and the injections of bacterial bodies, living or killed, or the products of their lysis, stimulate the formation of various antibacterial substances—agglutinins, bacteriolysins, bacteriocidins, precipitins, opsonins, etc. These are found in the circulating blood, and, as noted in the preceding paragraph, are developed by the action of the toxins, etc., on certain special cells—possibly of the reticulo-endothelial system— as well as on the leucocytes themselves.

3. **Allergic Response.** It has been proved that, in the course of an experimental bacterial infection, the tissues may become so sensitised that a further dose of the same organism, which at the time of the primary inoculation might have produced little or no obvious effect, gives rise to a severe reaction. This allergic response occurs also in disease, and it is thought by some that the joint-affections in the relapses of acute rheumatism are, at all events partly, of this nature—the tissues having become sensitised by the original attack. This subject is dealt with on p. 135.

IMMUNITY

The existence of immunity, or resistance against infection in individuals, species and races, is well known, and some of the more important facts bearing on this problem must be considered in dealing with the causes and effects of disease. In man, this power of resistance varies in individuals, and probably is never absolute. Moreover, immunity is *not* developed where the body and its tissues have not learned to resent the presence of a rebel element such as the cancer-cell, or—though in lesser degree—the intrusion of some invaders such as, say, the *Treponema* of syphilis. Liability to, and resistance against, viral infections are considered in Chapter IV, p. 96 *et seq.*, and on p. 133.

In natural immunity, the defences concerned may be those which can prevent the invasion of the tissues by bacteria, viruses and other micro-organisms: or which are able to counter-attack and repel these micro-organisms, especially bacteria : or neutralise or destroy their products, after these have gained access to the tissues.

An intact skin-surface, though less efficacious against penetration by certain viruses than against bacterial attack, will hinder and usually entirely prevent the invasion of **bacteria** which have become lodged on it. Though this hindrance is largely mechanical, it is not wholly so. Leonard Colebrook, London, and others have shown that the bacteria deposited on the skin are actually killed, or at all events their numbers very considerably reduced, in a comparatively short time. This local destruction of bacteria takes place, not only on the surface of the skin, but on various other body-surfaces, such as the conjunctiva, the mucous membranes of the nose, mouth, nasopharynx, intestinal tract, genital tract, etc. Each of these surfaces has a more or less specific " normal " bacterial flora, and this flora is very similar in different individuals. It has been shown by various experimenters that, if *foreign* bacteria, *i.e.*, bacteria other than those of the normal flora, are introduced on these surfaces, they do not grow or flourish. There is some factor, the nature of which is not fully understood, which prevents colonisation by these *foreign* bacteria, but has no inhibitory effect on the colonisation of what may be called the *home* bacteria or commensals.

Alexander Fleming's work at St. Mary's Hospital on the **lysozyme** in tears and in nasal secretion[1] indicates one method by which this destruction takes place. He has shown that this substance in high dilution brings about the lysis of certain bacteria, but its action is limited, and many bacteria which can normally be recovered from the skin and other surfaces are not susceptible to the action of this secretion.

The salivary secretion is inimical to the life of some bacteria, *e.g.*, the meningococcus, but harmless to the normal flora of the mouth ; and the gastric secretion, with its high acid-content, destroys many of the bacteria which enter the stomach, and prevents them from infecting the intestine.

These and other natural defences play an important part in both local and general resistance to the lodgment and invasion of pathogenic bacteria, but it is difficult in any given example to estimate their real value as protective agents. They frequently fail, and the protection has to be carried out by a second line of defence—the cells of the body, and the products (**antibodies**) of the cellular reactions to bacteria and toxins.

Cellular Action. Phagocytosis. The phagocytes play an extremely important part in the destruction of bacteria which have invaded the body-tissues. As a result of such invasion, an army of phagocytes, at first mainly of the polymorphonuclear type, appears at the site of lodgment of the bacteria. The bacteria are, in many cases, ingested and digested by these phagocytes, possibly aided by the action of substances (**opsonins**, etc.) found in the plasma, and which have some sensitising or other injurious effect on them (pp. 126 and 133). Phagocytosis is less effective if the organisms have a high degree of virulence, or if they are capsulated. In such conditions, the bacteria enter the lymph-channels and lymph-nodes, the liver and spleen, where they are attacked by other phagocytes—the cells of the reticulo-endothelial system—or they may enter the blood and produce septicæmia or pyæmia.

Antitoxins and Antibacterial Substances. Freshly-drawn blood-serum of healthy individuals has the power of inhibiting the growth of, agglutinating and actually destroying, some pathogenic bacteria, and of neutralising toxins. The substances which produce these reactions may be natural constituents of the blood or may have been developed by previous infection or subinfection, *i.e.*, a " sub-clinical " infection, not intense enough to produce obvious disease, but capable of stimulating the production of immunising substances.

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[1] " Remarkable Bacteriolytic Element found in Tissues and Secretions," *Proc. Roy. Soc.*, B., 1922, **93**, 306.

Acquired Immunity. When a patient recovers from certain infections, such as typhoid fever, he is usually resistant to subsequent attacks. This acquired immunity may be produced artificially in the lower animals by inoculation on one or more occasions with suspensions of the causal organisms, living or dead, or in man by the injection of the dead bacteria in the form of a " vaccine " (see below) : or in some instances with the products of bacterial growth (toxins): or again, as in the original " Jennerian vaccination " against smallpox, by the use of the living virus of cowpox. This **active type** of acquired immunity, in which the antibody-producing tissues are sensitised and their specific reactive power is stimulated, develops in some four or five days and increases for fourteen to twenty-one days. The immunity may last for years, but usually it gradually weakens and ultimately disappears. The sensitisation, however, may last for long periods, and, during this time, a small dose of the specific antigen may bring about a rapid rise in the production of antibody. The serum from such an immune animal contains various kinds of antibodies and its injection into another animal will produce a **passive immunity** in the latter. This passive immunity is of only short duration, the immune-serum injected being rapidly excreted.

Individuals differ in their immunological response to the same organism, and likewise the response to different organisms varies widely. For example, enteric bacteria have a high, and tubercle bacilli a low, antigenic value ; and, therefore, in producing active immunity, it is necessary so to control the degree of infection or intoxication as to avoid severe reaction. If the reaction is too intense, a less marked degree of immunity results. The production of immunity is more pronounced and more rapid in acute than in chronic cases.

It is obvious that active acquired immunity is useful mainly as a **preventive** measure. In many acute infective diseases, where the bacteria are multiplying rapidly or where bacterial products are causing acute toxæmic symptoms, it may seem unreasonable to introduce more of the poison in the hope of arresting the progress of the infection, and yet many workers of experience claim that, even in acute infective diseases such as pneumonia or streptococcal septicæmia, the introduction of the causal organism as a vaccine may be beneficial. In less acute forms of disease, or in more or less localised infections such as boils and pustules, the use of vaccines, made from dead cultures of the causal organisms, has proved of great value. The view generally held is that the vaccines act on cells which have not been fully or sufficiently stimulated by the bacterial products resulting from the disease itself, and that this additional stimulation leads to increased phagocytosis and increased production of antibacterial bodies.

The production of passive immunity is used for both the **prevention** and **cure** of disease. For instance, when an individual is known to have been exposed to infection with the bacillus of diphtheria and there is insufficient time in which to immunise him actively, he may be rendered temporarily passively immune within a few hours by an injection of diphtheria-antitoxin. It will be noted that passive immunity is usually artificially produced, but antibodies can be transferred naturally from one individual to another, as from mother to fœtus, or in the drinking of cows' or goats' milk containing brucellar agglutinins.

Antigens and Antibodies. The substances capable of stimulating the cells of the host to produce antibodies are known as **antigens,** and as a general rule they must be introduced parenterally, *i.e.*, into the living tissues directly by some channel other than the alimentary canal. They are diverse in their nature. They may be bacteria (living or dead), bacterial products (toxins and toxoids), red blood-corpuscles, cells of various organs or tissues foreign to the animal inoculated, milk, egg-albumin, etc. With a few possible exceptions, they are all protein in composition, or at least substances of high molecular weight, and must be foreign to the animal inoculated. Thus, human red corpuscles will produce in a rabbit an antibody (**hæmolysin**) which will act on human red corpuscles, but which will have no action on the erythrocytes of the rabbit, nor would the injection of the red corpuscles of a rabbit into another rabbit produce an antibody of any kind. Experimentally, the direct inoculation into the blood or tissues is the most rapid and effective method of stimulating the production of antibodies, though it is claimed that this can also be done by ingestion or inhalation. **Antibodies** may be defined as those substances which appear in the blood of man and animals as the result of the introduction of an antigen into the blood or tissues, and which can be shown to react in some definite way with that antigen. Though these antibodies are not all of the same nature, they are each specific for the particular antigen which is responsible for the production of that antibody. Some, the **antitoxins,** act by neutralising and rendering inert the corresponding antigenic toxins; others, the **agglutinins** and **precipitins,** when brought into direct contact with their antigens, produce the reaction of visible agglutination or precipitation of their respective antigens; whilst others act only indirectly after union with a third substance (**complement**) present in the blood of normal animals, and are called **immune-bodies, sensitisers** or **amboceptors.** They sensitise the antigen so that union takes place between it and the complement and amboceptor, with resulting lysis of the antigen. If the amboceptor is specific and the antigen bacterial, bacteriolysis occurs; if the antigen consists of red corpuscles, hæmolysis is seen.

Antitoxins. The antitoxins used in the treatment of diphtheria, tetanus and other toxic infections are present in the sera of horses or other animals immunised by repeated injections of the toxins prepared by growing the specific organisms in an appropriate fluid medium and then freeing the fluid, which contains the toxin, from the micro-organisms by filtration. Immunity to such bacterial **exotoxins** is due to the presence in the circulating blood of antitoxins, and its degree depends on the extent to which circulating toxins can be neutralised by these antitoxins. The antitoxins may be developed as the result of an acute infection, or of a subinfection, *e.g.*, from a carrier, or may have been produced by an experimental injection of a toxin or a modified toxin—a **toxoid.** This immunity can be transferred from one animal to another by injecting the blood of an immune animal into a non-immune one, or by passage into the blood through natural channels, such as the placental vessels in the transference from the mother to the fœtus *in utero.* This passive transference is the basis of the antitoxic treatment of diphtheria, tetanus, scarlet fever, staphylococcal infections, botulism, bacillary dysentery and gas-gangrene. Active immunisation by the injection of toxins, toxoids and toxin-antitoxin or toxoid-antitoxin mixtures, on the other hand, is a prophylactic measure for the production of antitoxin in and by the individual himself, and has proved of great value in the prevention of epidemics.

Agglutinins. An antigen composed of formed elements such as bacteria produces, on injection into animals, an antibody which, in a salt-solution of suitable strength, causes a visible agglutination or clumping of a previously uniformly-distributed suspension of the homologous antigen. The clumps so produced are gradually precipitated, but the viability of the bacteria is not destroyed. Freshly-isolated strains of bacteria are sometimes inagglutinable, and, in such instances, the capacity of becoming agglutinable is established only after several generations of subculture. A quantitative measurement of the agglutinating power of a specific serum is made by testing progressive dilutions of the serum with a constant suspension of the antigen in physiological saline. The highest dilution in which the reaction occurs is called the " titre " of the serum for the particular suspension used. The presence of salts, as electrolytes, is necessary for the occurrence of agglutination.

The agglutinins produced against any individual type of organism are complex, since the antigens stimulating their production are usually multiple. As a rule, the major fraction of the agglutinins is specific for and capable of reacting with only one species of organism, but there is a minor part which reacts not only with the specific organism but with other allied species. This minor fraction is termed a " common " or " group- " agglutinin. The degree to which specific and group-antibodies are produced varies with different species of organism and even with individual types or strains of the same species, but it may be accepted as a general rule that a given antiserum reacts more rapidly and possesses a higher titre with its own (homologous) organism than with the other closely related (heterologous) organisms.

Agglutination-reactions are utilised for the diagnosis of disease in two ways. Firstly, the final criterion for the identification of many pathogenic organisms isolated from the body is their agglutinability by specific agglutinating sera, *i.e.*, the sera of animals which have been immunised with a known variety of bacteria. Secondly, the reaction may be used as in the " Widal " or, to give credit to the pioneer workers, the " Grünbaum-Durham reaction " to demonstrate indirectly the presence of a micro-organism in the body of the patient and its causal relation to disease by demonstrating in his serum the presence of agglutinins specific for that micro-organism. Thus, after some seven or eight days from the onset of an attack of typhoid fever, the patient's serum will, in the majority of cases, agglutinate the strain of typhoid bacillus causing the fever, and the agglutinating titre will within certain limits tend gradually to increase from day to day. These agglutination-reactions must be controlled carefully, for difficulties in the interpretation of the results arise from the presence of group-agglutinins as well as the specific agglutinin, from variations in the cultural characters and the antigenic structure of the causal bacteria, and from the presence of agglutinins resulting from previous attacks of the disease or from inoculation with vaccines, *e.g.*, T.A.B. vaccine (a vaccine containing *Bact. typhosum* and *Bact. paratyphosum A* and *B*). For further information on the antigenic structure of bacteria in its relation to agglutination and on the methods used and the precautions necessary to attain accurate results in the various tests, readers are referred to text-books on bacteriology and immunology.

Precipitins are antibodies produced in disease or by the immunisation of animals with filtrates of fluid cultures of bacteria, or by subcutaneous or intraperitoneal inoculation with milk, blood, white-of-egg or other substance rich in albumin. When the serum containing the specific precipitins is added to the fluid containing the substances which incite their production, a cloudiness and, later, a precipitate is formed. The reaction is closely related to agglutination, though no organisms are present. The precipitin-reaction has been employed and is useful in medico-legal work for distinguishing human blood-stains on clothing, etc. The serum of an animal immunised with human serum gives a pronounced reaction with human blood, a slighter reaction with the blood of the anthropoid apes and practically no reaction with the blood of other animals. The reaction takes the form of an opalescent ring of precipitate at the junction of the two fluids. Precipitins along with their homologous antigens can also fix complement, and tests utilising this principle are even more delicate than the original precipitin-reaction itself.

Immune-Bodies (Bacteriolysins and Hæmolysins) and Complement-Fixation. Whole blood when freshly withdrawn is capable of destroying certain bacteria. This power of destruction seems in part to be due to the presence of substances of the nature of **enzymes** and their action in aiding phagocytosis, and possibly also in part to the composition of the bacterial cell. It is not a true bacteriolysis. Pfeiffer and his colleagues showed that, if cholera vibrios were injected into the peritoneal cavity of a guineapig which had been immunised against these bacteria, the organisms lost their motility, gradually became granular and broken up into irregular droplets and, finally, underwent solution or **lysis.** This same reaction can be seen if the immune-serum of the guineapig is mixed with the cholera organisms on a slide. In the experiments of Pfeiffer, the specific antibody which had been developed in the immune-serum (**bacteriocidin** or **bacteriolysin**) did not lyse the bacteria or antigen directly. It first united with the bacteria, and the combined product was then acted upon by **complement,** which is a non-specific constituent of all freshly-drawn sera, whether normal or immune. When complement is added to a mixture of antigen and its homologous antibody, a union takes place, or, as it is usually expressed, the complement is **fixed** or **adsorbed.** Neither the antibody alone nor the complement alone can kill or lyse the antigen. The presence of all three substances, antigen, homologous antibody and complement. is required to produce the bactericidal effect, with the concurrent **fixation** of complement. The antibody may therefore be regarded as sensitising the antigen to the action of the complement, and a sensitised antigen is thus merely an antigen to which its homologous antiserum has been added. Formerly, antibodies were known as "amboceptors," owing to the belief that they linked the antigen to the complement. The optimum temperature for the fixation of complement is 37° C. and, as the temperature falls below that figure, the reaction becomes correspondingly slower. Even at 37° C. the complete reaction may occupy one hour. There is an important difference between the two serum-constituents taking part in these reactions. The complement, which is present in normal serum, is **thermolabile,** *i.e.*, it is destroyed by exposure to 55° C. for half an hour ; but the antibody (immune-body or "amboceptor") is **thermostable,** *i.e.*, it resists a similar exposure to that particular temperature.

A result analogous to that produced in bacteriolysis is obtained if the antigen is composed of the red blood-corpuscles or tissue-cells of one species of animal and the antibody is contained in the serum from another species which has been immunised by means of this antigen. Such a serum will be hæmolytic or cytolytic to its corresponding antigen in the presence of complement.

The principle of complement-fixation tests, as used in diagnosis, is that a specific antibody in a serum can sensitise a homologous antigen only, and that complement can aid in the lysis of **sensitised** cells only, or, in other words, the complement cannot be used up by or fixed to non-sensitised antigen. In a mixture containing antibody, heterologous antigen and complement, the last of these, *i.e.*, complement, will remain free to act on any homologous antigen which is introduced at a later time. Therefore the presence or absence of free complement in a mixture of antibody, antigen and complement, can be utilised to determine whether the antibody and antigen are homologous or heterologous. The complement-fixation test is used mainly for the serological diagnosis of syphilis (Wassermann reaction), hydatid-disease, gonorrhœa and tuberculosis.

Opsonins[1] (*see also* pp. 126–7). Normal blood-plasma or the serum derived from it[2] acts on bacteria in such a way that they become a more easy prey to the phagocytes. The substance in the serum which exerts this influence is known as opsonin. In normal blood, this opsonin is thermolabile and is destroyed by exposure to a temperature of 55° C. In the course of immunisation, a thermostable opsonin is developed which, unlike the opsonin of normal blood, can act in the absence of complement. These immune-opsonins seem to have an influence in increasing active phagocytosis and the consequent destruction of organisms, changes which were regarded by Metchnikoff as the main factor in artificial immunity. They resemble, if they are not identical with, the bodies called **bacteriotropins** by Neufeld and Ripman. These unite with the antigen, and apparently so alter the condition of the cell-membrane as to make the bacterial cell an easier prey for the leucocytes.

Leucocytes which have been washed in saline to free them from serum possess practically no phagocytic power when incubated along with suspensions of bacteria. When, however, a normal serum, which contains opsonins and complement, is added to the leucocytes, they ingest the organisms readily, and this power is greatly increased by the presence of an immune-serum containing immune-opsonins in place of the normal serum (*cf.* also pp. 126 and 128).

Anti-viral Immunity. Though our knowledge of the reactions of viruses on the body and their antigenic structure is still imperfect, the evidence so far available points to the probability that no essential difference exists between the mechanism of the production of antiviral and antibacterial immunity. The tissue-invasion in viral disease is similar to that occurring in bacterial infection, and, though the lesions produced may differ in some respects, the essential changes—inflammation, necrosis and proliferation—are much alike in both. One characteristic difference is the tendency in viral disease to the presence of inclusion-bodies in certain cells, and this characteristic may account for the selective localisation of such viral diseases, and it may also have some bearing upon the mechanism of production of antiviral immunity.

The common viral diseases of man: smallpox, measles, chickenpox and mumps, have the power of conferring immunity on the individual attacked, which, in the majority of instances, continues throughout life; but this is not true of all such diseases, for attacks of the common cold or of influenza either confer no immunity at all or an immunity of a very temporary character, and these varieties of viral infections thus resemble the bacterial diseases, in which the transient nature of the immunity is characteristic and passes off in a few weeks or months. When the antigen is a toxin or a modified toxin, as in diphtheria or tetanus, the lasting character of the immunity is more pronounced.

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[1] From Greek, *ὀψώνιον*, opsōnion, victuals or provisions, from the root ΠΕΠ, *PEP*, as in *πέσσω*, *pessō*, Attic *πέττω*, *pettō*, later *πέπτω*, *peptō*, I cook or prepare for eating; hence also *ὄψον*, *opson*, meat prepared daintily (as with sauce) for eating.

[2] The term " serum " is often used rather loosely for either " serum " or " plasma."

Active Anti-Viral Immunity is conferred in the same way as active immunity against bacterial infection, *i.e.*, by a typical single attack of the disease: by one or more mild infections without symptoms of the disease: or with symptoms insufficiently pronounced to attract attention. Further, active immunity may be induced artificially by scarification with, or by injections of sublethal doses of, the active living virus modified by passage, or by the initial injection of a fully-attenuated virus, followed by injections of progressively less attenuated strains until such a degree of resistance has been established that an active virus can be injected without producing any serious results. The classical example of the modification or attenuation of a living virus by passage through a series of less susceptible animals is that seen in the instance of vaccinia or cowpox and the original "**vaccination**" of Jenner—in which the lymph from the cowpox-vesicles of a calf inoculated with this milder form of the disease is utilised to protect the human subject against variola or smallpox, a more virulent and dangerous form of the same disease. The work of Pasteur in conferring immunity against hydrophobia, by repeated injections of attenuated vaccine produced by the drying of rabbit-cord virus, is another example. Whether, as in the case of bacteria, an effective immunity can be conferred by injections of virus completely attenuated or killed by heat, is uncertain. The real difficulty in solving this question is that there are no criteria by which the death of the virus and the retention of its antigenic power can be definitely established. The degree of immunity-reaction produced by the use of attenuated virus varies widely in different diseases, and experimental work suggests that an attenuated virus will produce some degree of specific resistance, but, if an effective immunity is desired, the initial injections must be followed by the injection of an active virus, the dose of the latter being such that no serious symptoms will develop in the partially-immunised animal.

Passive Anti-Viral Immunity. The use of anti-viral serum in certain diseases in man, such as poliomyelitis in its earliest stage and measles, has proved to be effective against the homologous virus. The antibacterial and antitoxic sera in common use for treatment of human disease are horse- or rabbit-sera, containing the antibody. To produce anti-viral immunity, the most effective results are obtained by the use of the serum of an animal of similar species to the host. Laidlaw and his colleagues found that an anti-distemper serum prepared in the dog will protect both dogs and ferrets against distemper-virus, but that the protection in the ferret is less effective and less uniform than in the dog, and that the vaccine made from ferret's tissues had little protective effect in the dog. In human viral diseases, anti-viral serum is usually obtained from the blood of persons who have had, and preferably who are just convalescing from, an attack of the disease for which the serum is to be used. Its use as a prophylactic and therapeutic agent is, therefore, still comparatively limited.

Allergy, Hypersensitiveness and Anaphylaxis. These terms are used indefinitely and it is hardly possible to differentiate precisely between them. They are concerned with a peculiar reaction which follows the injection into the tissues of a second dose of a foreign protein or its absorption from the mucous membrane into the body of an animal previously sensitised to that particular protein. The sensitisation may have been produced by a previous injection of a serum for prophylactic, therapeutic or experimental purposes, or by a previous natural infection. There is a form of natural hypersensitiveness in which constitutional disturbances and skin-rashes follow the ingestion of certain foods. The mechanism concerned in such cases is probably of a different nature from that which acts in protein-sensitisation (*see* pp. 136–7).

Richet (1907) observed that dogs to which he gave a **second** injection of the extract of certain actinozoa (sea-anemones, etc.), had, instead of developing the expected increased resistance usually produced by a previous sublethal dose, actually become **more susceptible** to the action of the toxic material; and, when given the second dose (known in these circumstances as the "assaulting" or "attacking dose"), might die suddenly with curious symptoms. To this reaction he gave the name **anaphylaxis.** Repeated experiments with consistent results obtained by various observers have proved that animals may be sensitised by the injection of any substance which has definite antigenic properties. In some animals, a single dose of the toxic material (antigen) is sufficient to sensitise; with others, and with some antigens, several doses and doses of varying amount may be required.

Though the sensitising-dose may be given by any route, that given for the purpose of producing the anaphylactic shock must be administered **parenterally,** *i.e.*, introduced into the blood-stream or into the tissues. It is *not* effective if given by the alimentary canal. After a sensitising-dose has been injected into an animal, a period of time, in the guineapig a minimum of ten days, must elapse before the symptoms of anaphylaxis can be produced by the "attacking dose." If the second injection is given *within* that period, no symptoms appear, and a condition of anti-anaphylaxis is established. Further, the anaphylactic shock in an animal which has been rendered potentially anaphylactic may be prevented by the injection of the antigen in doses less than those which are necessary to produce the symptoms. The animal is then said to be **desensitised.**

Whatever antigen is used, the symptoms and lesions of anaphylactic shock are constant for any given species of animal, but may differ in different species. The animals may exhibit dyspnœa, œdema, vasomotor paralysis, and impairment of cardiac contractility. In the guineapig, dyspnœa is a marked feature, the alveoli of the lungs being greatly distended, *i.e.*, acutely emphysematous, owing to contraction of the muscle in the walls of the bronchioles preventing the egress of air. In the rabbit, the reaction follows with less certainty, larger doses are necessary, and pulmonary distension is absent. There is contraction of the pulmonary arterioles, with extreme dilatation of the right side of the heart and acute cardiac failure. In the dog, there is a rapid fall in blood-pressure, engorgement of the liver, and incoagulability of the blood. In a small minority of cases in man, death may follow a few minutes after the injection of serum—even a first injection. This is a true anaphylactic shock—a "foreign-protein susceptibility." An analogous condition, characterised by an urticarial skin-rash, swelling and pains in the joints, slight, or in some cases more marked, pyrexia, is sometimes produced in man by injections of normal horse-serum or of antitoxic or antibacterial sera, the foreign protein in the serum being the substance initiating the reaction. This condition is called **serum-sickness,** and the symptoms are associated in certain individuals with a special hypersensitiveness to horse-serum. In the majority of such cases, there is an incubation-period of from eight to ten days between the injection of the serum and the onset of symptoms. At the site of injection there is swelling due to inflammatory œdema, and the lymph-nodes draining the area become enlarged and softened.

Specific hypersensitiveness may develop during the course of a natural or experimental bacterial infection, and is termed "**allergy.**" A familiar example is the occurrence of local inflammatory swelling and pyrexia which follow the injection of **tuberculin** or **mallein** into individuals or animals infected with tuberculosis or glanders respectively, phenomena, the production of which can be utilised in the diagnosis of these diseases.

As previously stated, it has been suggested that the relapses and the joint-swellings in **acute rheumatism** and the acute attacks of **gout** are in reality allergic reactions. The inoculum by means of which the anaphylactic shock or the allergic reaction is brought about must be homologous in constitution with the antigen which has produced the sensitisation. Thus a guineapig sensitised with horse-serum will show the anaphylactic phenomena only if the second injection is also of horse-serum—*not* if it consists of human serum.

The effects of anaphylactic shock have been thought to be similar to those produced by histamine-poisoning, and it has been suggested that the disturbance of the cells by the introduction of the anaphylactogen might liberate a histamine-like substance which, acting on the bronchial and other muscle-fibres, brings about the shock (*cf.* p. 183). Variations in the reaction are due to differing factors, such as the species of the animal, its degree of individual hypersensitiveness, the nature and dose of the antigen (anaphylactogen), and the method (route, site, etc.) of inoculation employed. Intravenous and intrathecal injections of large doses are liable to produce marked reactions. Apart from actively-acquired hypersensitiveness, there is a passive, more or less transient, form produced by the injection of the serum of a sensitised animal into a healthy one.

Hypersensitiveness is a matter of considerable practical importance in serum-therapy. Its presence may be detected by the occurrence of an urticarial wheal following the intradermal inoculation of a small dose of the serum which it is intended to inject. Hypersensitive individuals may be desensitised by means of very small and repeated doses of the serum.

Various hypotheses have been advanced to explain these phenomena, but it is sufficient for our purpose here to say that the fundamental mechanism is a union of, or contact in some way between, antigen and its specific antibody.

Idiosyncrasies. Certain persons, when brought into contact with some particular substance, exhibit symptoms which indicate a **hypersensitiveness to that substance.** The substances which may evoke the response are mostly **foreign proteins.** The symptoms vary, but they may be those characteristic of such conditions as hay-fever—produced by the action of pollens of various grasses—asthma from other varieties of pollen, horse-dandruff, or hair or fur of animals—and skin-rashes, especially urticaria, from the ingestion of foods such as shellfish, eggs, milk, strawberries, etc. Many of these symptoms—the bronchial spasm of asthma, nasal and conjunctival irritation, and skin-eruptions—are identical with those of anaphylaxis. In some of these conditions, such as asthma and hay-fever, evidence of the presence of such hypersensitiveness may be elicited by introduction of a suitable extract of the causal agent—pollen, dandruff, etc.—intradermally. At the site of injection, redness and swelling, or it may be an urticarial wheal, are produced. Further, if a minute quantity of the serum from a passively-sensitised patient is injected intradermally into a normal individual, he becomes, after a sufficient interval of time, sensitised. This is proved by the fact that, if he receives a subsequent injection of the particular substance which produced the original sensitisation, he will develop the characteristic skin-reaction. The view that **increased specific capillary permeability** is the fundamental physiological change in protein-sensitisation, to which all other anaphylactic reactions are secondary (Manwaring *et al.*, 1923) [1], is gaining ground and is supported by the finding that some 50 per cent. of allergic children exhibit such abnormal capillary fragility (Rapaport and Klein, 1941), and often benefit by the administration of **vitamin P** ("citrine," a flavone-glucoside prepared from lemon-juice by fractionation). (*See* p. 443.)

To such idiosyncrasies the term **Atopia** ("strangeness" or being "out of place") is applied. The passive transference of this hypersensitiveness depends on the presence of an antibody in the blood of the hypersensitive individual.

The acute vomiting and other gastro-intestinal disturbances, which in some persons are associated with the ingestion of particular foods, seem in some respects to be different in their mechanisms from those responsible for anaphylaxis. But the occurrence of reactions, especially in cases where skin-sensitivity can be transferred to normal individuals, suggests that the underlying mechanism in the two conditions is similar.

Local Immunity. There is a type of immunity which is not dependent upon the presence of antibodies in the blood, and is termed local immunity. It has been noted that an area of skin which has been the site of erysipelas is definitely more resistant to a subsequent injection of the causative streptococcus, and, further, there may be, in the same individual, the simultaneous occurrence of a recovered resistant area and of another actively-spreading one. Thus, a local immunity may exist in the absence of a general immunity. The evidence suggests that non-specific factors are responsible for this type of immunity, and that the cellular reactions which follow the initial inflammatory lesion and which persist for some time are the barriers against re-infection.

The contrasting phenomenon of **locally-increased liability to infection** is seen in the tendency in some individuals to recurring inflammatory attacks at, say, the junctions of mucous membranes and skin-surfaces, for example at the angles of the mouth. Stannus [2] believes that such individuals may be suffering from varying degrees of **vitamin-deficiency** and describes their successful treatment with certain elements of the Vitamin-B complex.

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[1] "Capillary Permeability in Anaphylaxis," by W. H. Manwaring, R. C. Chilcote, and V. M. Hosepian, Stanford University, U.S.A., *Jour. Amer. Med. Assoc.*, 1923, **80**, 303.

[2] "Pellagra," by Hugh S. Stannus, London, *Lancet*, 1940, *i*, 352. (*See also* our Chapter on Vitamins, p. 445.)

CHAPTER VI

HEAT-REGULATION AND FEVER

It is difficult for us now to realise that the scientific recording of the body-temperature in disease has come into general use only since it was advocated by Clifford Allbutt [1] in 1870, when the first pocket clinical thermometers were made at his suggestion. Allbutt himself pointed out, however, that Dr. J. Currie,[2] of Liverpool, was, in 1797, perhaps the first to make use of the then newly invented thermometer. " A careful attention," wrote the latter, " to the changes of the animal heat, and to the state of those functions on which it depends and by which it is regulated, though more requisite in febrile diseases, perhaps, than in others, is, however, of importance throughout the whole circle of diseases."

The term " fever " is used commonly to imply a rise of temperature only, but we prefer to use the word in its much wider significance as implying a disorder in which the rise of temperature (pyrexia) is only one feature. The pyrexia, the wasting, the alterations in secretion and absorption and other factors constitute the " fever " and may be all produced by the action of some specific agent, *e.g.*, bacteria ; and it is, therefore, obvious that the rise of temperature, though an important and very definite indication of the action of some infective agent, is nevertheless, in the majority of cases, only one manifestation of that action.

I. HEAT-REGULATION

In the normal individual, the temperature is regulated by a balance between heat-production and heat-loss, but the exact mechanism of its regulation is not fully understood.

(*a*) **Heat-production** takes place in the skeletal muscles, and to a less extent in the glandular organs, such as the liver, suprarenals and thyroid. When the body is at rest, the metabolic activity, *i.e.*, the rate of oxidation in the tissues, is so adjusted as to maintain an appropriate internal temperature. Muscular and glandular actions are both characterised by increased oxidation in the tissues and a consequent rise in temperature. Similarly, cold weather, by encouraging muscular movement and stimulating the production of adrenalin and possibly of the thyroid secretion, brings about increased metabolism, and also causes constriction of the cutaneous arterioles and perhaps capillaries, increasing the amount of blood in the internal organs.

(*b*) **Heat-loss** is due mainly to radiation and convection and to evaporation of sweat from the skin, but the setting free of carbon dioxide from watery solution into the expired air and the using up of heat in warming food and air which is ingested or inhaled acts in the same way, but to a lesser degree, a certain amount of heat being also lost in the fæces and urine. According to Starling, the loss of heat by radiation and convection and the evaporation of sweat from the skin amounts to 80 per cent. of the total in a normal individual, while 15 per cent. is lost in respiration and 5 per cent. by the warming of ingested food and inhaled air.

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[1] " Medical Thermometry," by T. Clifford Allbutt, *British and Foreign Medico-Chirurgical Review*, 1870, **45**, 429 and **46**, 144.

[2] " Medical Reports on the Effects of Water, Cold and Warm, as a Remedy in Fever and other Diseases," Liverpool, 1797.

The raising of the temperature of the surface of the body, especially if that higher temperature is maintained for some time, causes a dilatation of the arterioles and capillaries of the skin, with consequent diminution of the volume of blood in the brain and internal organs. Convection and radiation can take place only if the temperature of the external air is lower than the body-temperature, for, in such a case, the layer of air in immediate contact with the skin becomes warmed, rises and is replaced by the colder air (convection). If the temperature of the body is equal to or lower than that of the external air, the only means of heat-loss is by evaporation.

Thus both in heat-production and heat-loss there are obvious reactions varying in character and degree in the different organs and tissues—the vascularity of the skin, the activity of the sweat-glands, the pulmonary ventilation, and the activity of the skeletal muscles and the secretory glands. These changes are all under the control of the nervous system, and, from both clinical and experimental evidence, it is apparent that interference with this control brings about a disturbance of heat-regulation (p. 144).

Daily Temperature. In a healthy person, the normal range of temperature in the mouth is from 96·7° F. to 99° F., and in the rectum 97·2° F. to 99·5° F. Further, the daily variation may be 1° to 1·5° F., and this is parallel with the alternate rise and fall in the rate of metabolism and the elimination of carbon dioxide. The temperature is highest in the evening and lowest in the early morning, higher in females and in the young than in males and older people, and there is greater variability in children than in adults. The daily variations are due mainly to the varying activity of the tissues. Thus, during muscular work, the maximum is reached ; whereas, during sleep, the lowest temperatures are recorded. Mere rest in bed lowers the temperature, and it has been shown that restlessness is accompanied by increased combustion and a corresponding rise of temperature.

It is a common experience that most people feel more uncomfortable in a warm, moist atmosphere than in a dry one, though the temperature of the latter may be much higher. Similarly, a cold, damp day is less invigorating than a cold, dry one. This is due to the fact that moist air is a better conductor of heat than dry air, causes an increase of heat-loss by convection and radiation, hinders evaporation and thus disturbs the normal balance between heat-production and heat-loss. If the external temperature is high and the air moist and still, the heat-loss by convection and radiation may cease, evaporation is hindered, with a consequent breakdown of the heat-regulating mechanism and a rise in body-temperature. There is usually a dilatation of the peripheral vessels and a lowering of blood-pressure. There may be disturbance of the cerebral circulation and the action of the heart associated with actual **heat-stroke** or **heat-collapse**. These results are more likely to supervene in individuals who are working hard and are unsuitably clothed.

This general experience has been confirmed by scientific investigation and particularly by the experiments of J. S. Haldane in the Dolcoath mine in Cornwall. Clothed in flannel drawers, canvas trousers, boots and stockings, he remained two hours eighteen minutes in this mine, in which the air was highly saturated with moisture (wet-bulb thermometer reading 93·6° F.), the external temperature high (dry-bulb reading 94° F.) and the air still. At rest, his pulse-rate rose to 164 per minute and his rectal temperature to 104·6° F. There was no rise of rectal temperature if the wet-bulb thermometer was not above 85° F., and, if the air was in motion, a reading of 93° F. was reached without an increase in body-temperature. During muscular work in still air the limit of wet-bulb temperature which could be borne without abnormal rise of temperature was much lower. The symptoms observed to accompany the rise of body-temperature were : (1) a marked increase in the pulse-rate, accompanied by throbbing in the heart ; (2) dyspnœa on any exertion ; and (3) a general feeling of exhaustion and discomfort.

The loss of sodium chloride associated with excessive sweating by those actively engaged where the temperature is high, and especially those exposed to radiant sources of high temperature, may produce the condition of **heat-cramps.** That salt-depletion is the important factor is shown by the preventive and curative value of provision of salt for workmen when such conditions prevail.

II. FEVER

In disease, pyrexia is one of the methods by which the body responds to infection and may be regarded as a reaction of a preventive or curative nature—the infective material producing metabolic changes in various organs and stimulating the development of antibodies or inhibiting the growth of, or even destroying, the infective agents themselves.

The heat-production and heat-loss are not balanced, the tissues have to adjust themselves to a temperature often much above the normal level, and as a result the heat-regulating mechanism becomes disordered.

In children, this mechanism is less stable than in adults, pyrexia is of commoner occurrence and may result from comparatively slight stimulation.

It is well known that a high temperature in a child may be produced by a minor infection, whereas in an adult it more usually indicates the presence of a gross pathological lesion.

During the course of many infective diseases, the temperature-chart and the general metabolism of the patient indicate the invasion of, and the subsequent action on, the body by pathogenic micro-organisms. The fever lasts for varying periods, and can usually be divided into three stages, which are well illustrated in a typical case of malaria, the **onset,** the **fastigium**[1] or **height,** and the **defervescence.** At the onset, the patient feels cold, shivers and may have well-marked rigors, the teeth chatter, the lips become blue and the arms and legs cold. There is increased metabolism and the internal temperature rises rapidly within fifteen or twenty minutes, reaching, it may be, 104° or 105° F. Gradually, the shivering ceases and the sensation of heat becomes more and more pronounced, until the patient feels burning hot. During this hot stage (fastigium), which may last four or five hours, the temperature reaches its maximum, the superficial vessels become dilated and the skin dry and hot. There is a loss of heat by convection and radiation.

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[1] Latin, *fastigium,* the top, roof or peak of anything, *e.g.,* the ridge of a house.

The hot stage is succeeded by the sweating stage, when the temperature falls rapidly (defervescence), and, in some cases, becomes normal or even subnormal.

These three stages may be noted in many fevers, though they may not be so pronounced as in malaria. The ushering in of the disease by a **rigor** [1] is very common, but sometimes the first stage may be one of marked mental depression, and, in children, not uncommonly, the rigor is replaced by a convulsive seizure. In all cases, however, the rise in the temperature is in the internal parts of the body, though, to the observer, the skin may feel quite cool.

The second stage may last only a few hours (as in malaria), a few days (as in pneumonia), or several weeks (as in typhoid fever). The skin at this stage is usually dry, but sometimes, as in rheumatic fever, there is much sweating.

The third stage—that of reduction of the temperature—may begin suddenly and proceed rapidly. Thus, in pneumonia, the temperature may fall several degrees in a few hours, constituting the so-called **crisis** (Fig. 62). In other cases, the termination may be gradual or by **lysis** (Fig. 63), the temperature falling, generally rising again and then falling slowly to or below the normal. In other diseases, *e.g.*, tuberculosis, typhoid fever, etc., the temperature may swing, the successive rises often occurring in the evenings, and the falls taking place in the mornings.

The type of pyrexia in different diseases is not uniform. It may be **continuous,** as in pneumonia and typhoid fever ; **remittent,** as in advanced tuberculosis ; or **intermittent,** as in recurrent or relapsing fevers (Figs. 64 to 68). There is no definite knowledge as to the cause of these variations, but it seems clear that they must have some relation to the action of the infecting agent on the cells of the body, in the rapid, slow or variable production of poisons and antibodies. The antibodies, if produced rapidly, may be sufficient in amount in a few days to neutralise the poisons and so produce a sudden fall of temperature.

Intermittent, **recurrent** and **relapsing fevers** are generally to be explained, either by a coincidence between the fever and the invasive and developmental stages in the causal organism, or possibly by variations in the production of protective substances. Thus, in malaria, the stage of high temperature corresponds with a definite stage in the life-cycle of the causal parasite. When this is completed, the temperature falls ; and, when it recurs, on the second or the third day, the temperature again rises ; and this alternate rise and intermission go on until the activity of the parasite is destroyed (Fig. 67).

Malta or Mediterranean fever and the closely allied **undulant** fever caused by infection with *Brucella abortus* have an irregular temperature-curve consisting of intermittent waves or undulations of pyrexia (Fig. 68). In the course of these infections, which may continue for long periods, the individual undulations of temperature may last for from one to three weeks, with an apyrexial, or a less intense pyrexial, interval.

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[1] Latin, *rigor*, stiffness from cold, from *rigeo*, to be frozen stiff.

The following temperature-charts, recording the morning- and evening-temperatures each day, will illustrate some of the points to which reference has been made :—

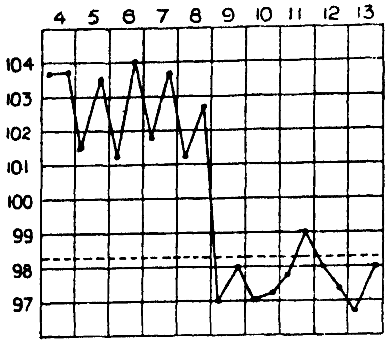


FIG. 62. Temperature-chart of a case of pneumonia, with crisis on the eighth day, showing continuous fever, then sudden fall by " crisis."

(NOTE.—Most commonly the crisis in pneumonia occurs on the seventh day.)

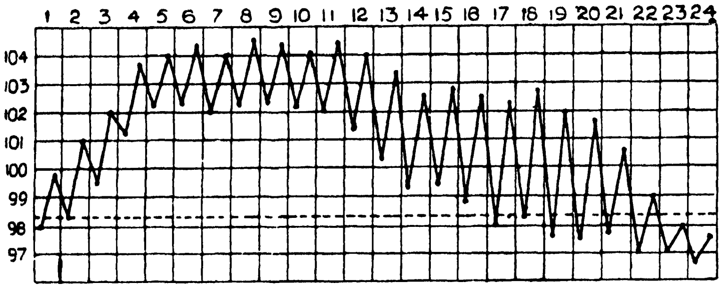


FIG. 63. Temperature-chart in enteric fever, showing gradual rise, continuous fever, then gradual fall by " lysis."

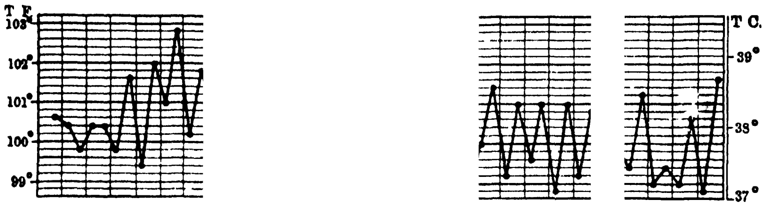


FIG. 64. Temperature-chart from a case of leukæmia, showing remittent type of fever.

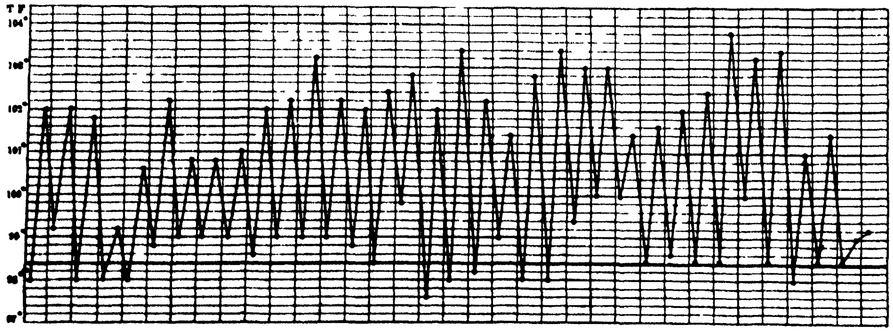


FIG. 65. Portion of the temperature-chart of a boy, aged five, the subject of tuberculous peritonitis, showing a " swinging " type of temperature.

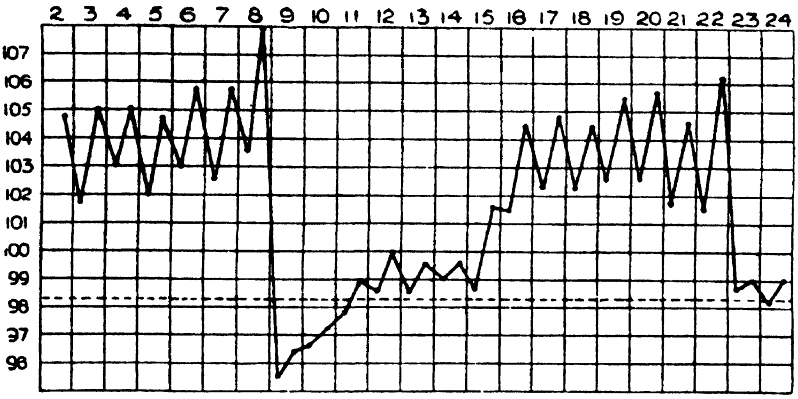
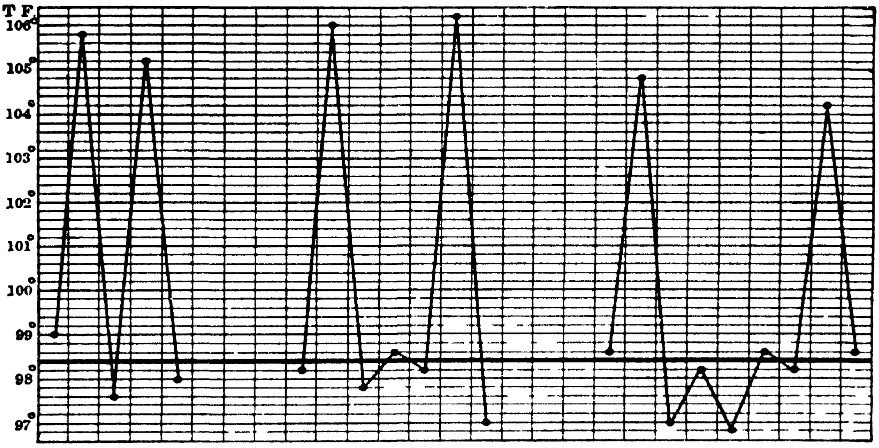


FIG. 66. Temperature-chart in relapsing fever.



Quotidian. Tertian. Quartan.

FIG. 67. Intermittent types of temperature in malaria.

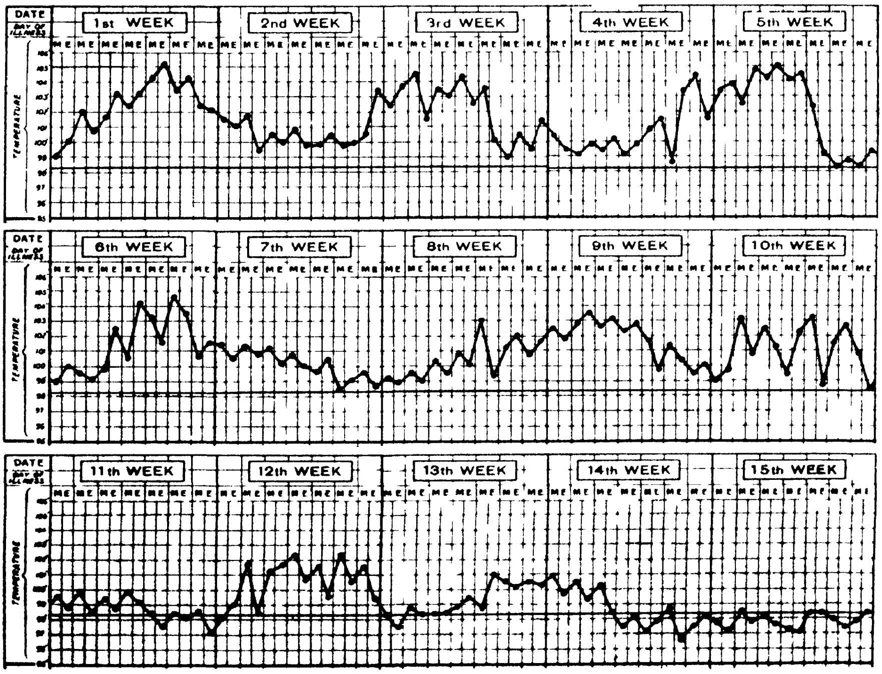


FIG. 68. Temperature-chart from a case of abortus (undulant) fever.

In **relapsing fever** (Fig. 66), due to infection with *Borrelia* (*Spironema*) *recurrentis*, the temperature rises as the parasites increase in number, and, when this increase has reached its maximum, the numbers again become reduced, and, coincident with this, there is a fall in temperature. It is generally held that protective bodies are developed during the attack, that these check the development of the micro-organism, and that a fresh attack is due to the decrease or disappearance of these antibodies.

Metabolism in Fever

In fever, increased metabolism is one of the most important features. According to Samson Wright, a rise of 1° F. in the internal temperature of the body increases the basal metabolism by 7 per cent. Thus in a case of pneumonia with a temperature of 105° F., there would be an increase of 50 per cent. in the patient's metabolism. But rise of temperature alone does not explain all the metabolic changes associated with fever. Many factors come into play and it is difficult to decide the main cause of febrile metabolism. Associated with the rise of temperature, the digestive and absorptive mechanisms are disordered, and the food taken in is not adequate to supply the needs of the individual, with the result that a call is made on the already stored food-elements in various organs and tissues. The carbohydrates in the liver and in the muscles are rapidly used up, and the body has to maintain itself on its own proteins and fats. The disintegration of these is shown by the excretion in the urine of abnormally increased amounts of urea, ammonia and other nitrogenous bodies, as well as of sulphates and phosphates. Albumin may also be present and abnormal pigments such as urobilinogen and urobilin,[1] and porphyrin (p. 227) from alterations in the blood and bile. There is diminution in the secretion of salivary and gastric juice, and alterations in the circulation and respiration. It is well known that toxins and other bacterial products, when absorbed, produce degenerative and destructive changes, such as cloudy swelling, fatty degeneration and necrosis, in cell-protoplasm, and that increased metabolism is a direct result. It seems, therefore, not unreasonable to assume that, in the early stages of fever, similar changes, though to a minor degree and with very little visible naked-eye changes, take place. In these early stages, contraction followed by dilatation of the peripheral vessels occurs, the pulse-rate is accelerated, the blood-pressure reduced, respiratory movements are increased, and there may be dyspnœa and hyperpnœa.

It has been shown that a rise of temperature acts on the sino-auricular node and probably on some cardio-accelerating centres in the brain, situated, it is said, in the region of the vagal nuclei, bringing about the more rapid action of the heart and increased pulse-rate.

The conclusion drawn from these facts is that the metabolic changes associated with fever are the combined result mainly of the pyrexia, the direct action of bacterial and other toxic bodies on the tissue-proteins, and the inadequate replacement-supply of proteins and other food-factors from outside. The increased pulse-rate, the respiratory changes, the restlessness, the depression, delirium, and other symptoms of this altered metabolism are believed to be due primarily to some disordered condition of the heat-regulating centres which are situated probably in the hypothalamic region of the cerebrum. The precise mechanism through which this control is exercised is still uncertain, but some actual damage to the heat-regulating centres themselves may occur in such cases.

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[1] Only traces of urobilin and its chromogen, urobilinogen, insufficient to affect the colour, are present in normal urine.

The degree of the pyrexia and the activity of the metabolic changes do not necessarily run parallel. There may be very moderate pyrexia with extreme metabolic changes, and the assumption, therefore, is that the nature of the irritant and the degree of susceptibility of the patient are important factors in the production of the disordered metabolism. The injection of foreign proteins, *e.g.*, bacterial vaccines, milk, peptone, etc., may in some individuals produce severe metabolic changes and high temperature, whereas, in others, very little reaction follows the injection. This "**protein-shock**" has been used extensively in the treatment of chronic bacterial disease and in many cases with considerable benefit. More consistently beneficial effects have been obtained with **autogenous bacterial vaccines,** but good results have also sometimes resulted from the use of vaccines which were non-specific for the particular disease involved. The explanation generally given of these beneficial results of treatment with bacterial vaccines, is that, during the pyrexia, antibodies are formed, and that these antibodies neutralise the detrimental action of the bacteria or the toxins which cause the disease. The pyrexia sometimes associated with the presence of tumour-growth or with the occurrence of non-infected areas of necrosis, is due probably to the absorption of the products of the breaking-down cell-proteins.

This "non-specific therapy" is also employed in the treatment of general paresis (pp. 1011 and 1015). Benefit has been obtained in many cases by the introduction of the living parasite of malaria into the blood and the production of an attack of malarial fever ; and the artificial induction of pyrexia by radiant-heat and other methods has also been employed for the treatment of paretic patients.

It has been thought that the dilatation of the superficial blood-vessels may be brought about by the liberation in the skin of histamine (*cf.* pp. 183–4) or a substance allied to histamine ("H") ; and it has been stated that, if the temperature of the skin is high, large amounts of this substance are set free and that even wheals and blisters may be produced. For further information on this point and also on the possible action of acetylcholine, readers should consult works on Physiology.

Heat-stroke—Heat-prostration. This condition occurs in very hot weather, and particularly in certain climates when the air is laden with moisture. It occurs usually in debilitated people, or in those undergoing great muscular exertion, especially if they are unsuitably clothed, *e.g.*, stokers, workers in hot, moist mines, or soldiers on the march. Nothing very definite is found at autopsy to account for such deaths. Rigor mortis is marked and sets in at once. The blood is fluid, but dark. Heat-stroke is the result of a disordered temperature-regulation. The hot moist external air prevents, or rather does not conduce to, the needful loss of heat by conduction and radiation. Evaporation also is hindered ; the internal temperature rises, metabolism is stimulated, with a resulting increase in heat-production. If this increase reaches a certain level, the blood-supply to the brain and heart may be so impaired that collapse and even death may take place.

Heat-stroke has been distinguished from **sunstroke** resulting from exposure, especially of the head and neck, to the direct rays of the sun ; and, in cases of death from the latter condition, there is generally found, at the autopsy, a congestion of the face and scalp, associated with hyperæmia and œdema of the meninges and brain. Some authors, however, regard this as a variety of heat-stroke. This view is all the more tenable since it has been shown that light-waves, including those of the ultra-violet regions of the spectrum, have but little penetrating power and cannot possibly reach the meninges. The heat-rays are therefore to be considered those of importance in the production of sunstroke. There is also probably a local release of energy in the form of heat due to transmutation of light-energy to heat-energy during the absorption of light. From the clinical side, however, there is some value in retaining the concept of " sunstroke," since meningeal irritation with slowing of the pulse may serve to differentiate it from other forms of heat-stroke. A persistently enhanced liability to recurrence is an important and little understood feature of sunstroke.

A Note on Certain Problems connected with Aviation

The following note merely suggests some of these and is inserted between these two chapters as it refers to the subject-matter of both.

At the great heights to which aeroplanes now fly—25,000 or 30,000 or even 40,000 feet or more (*i.e.*, some five, six, or seven to eight miles : the present "record" being 56,046 feet, or over ten miles)—serious problems of diminished air-pressure and especially **decreased oxygen-tension,** as well as of the intense **cold**, are involved, and also the question of "**decompression**" and the prevention of the too rapid escape of the gases dissolved in the blood on sudden change of altitude (in which connection see also under " Caisson-Sickness," p. 169). Quick turns made when flying at high speed, for example in pulling suddenly out of a "power-dive," "**centrifugalise**" the organs and tissues of the body and produce phenomena such as "**black-out,**" *i.e.*, temporary, but complete, loss of sight—whether from interference with the blood-supply of the retinæ or of the cortical occipital or other visual centres, is not yet known. There is also the phenomenon of **loss of consciousness** on suddenly leaving the 'plane and its oxygen-supply when " baling out " and making a parachute descent, during which, also, the atmospheric pressure encountered is rapidly rising.

These and other problems, physical and psychological, are exercising the minds of physiologists, but pathologists also must be alive to the possibility of damage, temporary or permanent, to delicate organs such as the brain, if sufficient preventive precautions are not taken.[1]

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[1] Consult "Principles and Practice of Aviation Medicine," by Harry G. Armstrong, Capt., Med. Corps, U.S. Army. Baillière, Tindall & Cox, London, 1939.

CHAPTER VII

DISTURBANCES OF THE CIRCULATION

Note. As cardiologists and clinicians in general have not yet adopted the new anatomical nomenclature which has been introduced in many anatomical schools, we propose still to employ the older terms. The new equivalents are **atrium** for *auricle*, **auricle** for *auricular appendage*, and so on.

In order to maintain the nutrition of the body at its highest level, various physiological functions must be satisfactorily performed, and the chief of these is the circulation. Any disturbance of this leads to nutritive changes ; and, if the disturbance be prolonged, permanent damage will be done to the cells and tissues of the body. For carrying on the circulation efficiently, in addition to normal control by the autonomic nervous system (p. 1190) and an adequate supply of adrenaline and other products of the endocrine organs and of vitamins in the food, at least three factors are necessary, viz., a normally functioning heart, healthy blood-vessels, and blood which is normal in quantity and quality. The relations between these three factors are so intimate that a disturbance of one practically always leads to some alteration in the others.

The Heart. Inflammation and various degenerations of the pericardium, myocardium, and endocardium give rise to disorders of the circulation, resulting in diminished arterial supply, engorgement of the venous system, capillary dilatation, devitalisation of tissues, cyanosis and œdema.

The Blood-Vessels. The elasticity, resilience and contractile power of the walls of the arteries are the principal factors in regulating the rate and the amount of blood flowing through them. If these properties are diminished or lost, dilatation of the lumen follows, and thickening of the inner coat may supervene. The propulsion of the blood is therefore not now aided by the contractility of the arterial walls, and the result is stagnation and stasis. Further degeneration takes place in the walls of the arteries, and this, by increasing the work of the heart, produces hypertrophy and dilatation in that organ.

The Blood. Any alteration in the quantity of the blood passing into a part is of very considerable importance, and it is obvious that this must be influenced largely by the two first-mentioned sets of factors, viz., any impairment in the function of the heart or of the blood-vessels, or of both. Morbid alterations in the composition of the circulating fluid have a deleterious effect on cell-nutrition in general ; and the resulting pathological changes are referred to later (p. 189 *et seq.*).

It should be noted, however, that, in the ultimate capillaries, the blood is separated from the tissue-fluids by a thin semi-permeable membrane—the endothelium—and that a similar membrane separates the lymph-flow from the tissue-fluids. A balance between these three fluids is established at a constant level by diffusion and osmosis. For the influence of the "permeability-vitamin" (vitamin P or "citrine") on the capillary-wall, *see* pp. 137 and 443.

Though circulatory derangements may be caused by mechanical obstruction and by inflammatory and degenerative changes, and though it is not always possible, in any given case, to assess the relative importance of each, those due almost exclusively to mechanical obstruction are most convenient for the study of these derangements.

Changes Dependent on Mechanical Obstruction. Mechanical obstruction to the flow of blood may affect the arteries, the veins, or both. If the obstruction is arterial, there is a diminished supply of blood to the tissues, with consequent impaired nutrition ; if venous, interference with the outflow of blood and engorgement of the drainage-area will follow. To the former condition of defective local blood-supply, the term **ischæmia**[1] is applied : to the latter, **congestion** or **hyperæmia.** The term **hyperæmia** is applied to conditions where the blood accumulates in an organ or tissue, either from an increased afflux or from a diminished outflow. It is true that the term " active hyperæmia " or " active congestion " is used to describe the condition produced by increased inflow of blood : and "passive hyperæmia " or "passive congestion " to that produced by diminished outflow ; but this distinction cannot always be strictly maintained, because under the term " active hyperæmia " are included those conditions in which the engorgement is due merely to a local dilatation of the minute vessels of an area, and in which there is neither increased afflux nor obstructed outflow. Though these terms must be retained, we agree with W. S. Greenfield and G. Lyon[2] that : " For conditions due to dilatation of the minute vessels of the part, the venules and capillaries especially, the term **congestion** would be convenient ; whilst those due to venous obstruction might well be called **venous engorgement,** and those associated with increased afflux of blood, **active hyperæmia.**"

VENOUS ENGORGEMENT, OR VENOUS OBSTRUCTION

If the veins become obstructed from any cause, and the inflow of blood still continues, the venous channels dilate, the engorged area becomes blue from a deficiency of oxygen in the blood (one form of " cyanosis "—*see* p. 158), and there is more or less interference with sensation. The results of obstruction may be local in distribution, where it is due to changes in or around the vessels, or may be general, as a result of central obstruction in the heart or lungs.

Local venous congestion may result from :—

1. Obstruction of the vein by ligature, by tight bandaging or by pressure from without by tumour or aneurysm.

2. Incompetence of the valves of the vein and thickening of one or more of its coats, sometimes associated with degenerative changes and deposits of lime-salts, with narrowing or dilatation of the lumen. These conditions may be aggravated by the anatomical arrangement of the vein, *e.g.*, the left spermatic vein—and by gravity.

3. Thrombosis, which may follow some local injury or degenerative change of the wall or obstruction of the lumen by portions of tumour-growth, parasites, or foreign bodies.

The phenomena and effects of the local venous congestion vary with the character and position of the obstructed vein, the degree of obstruction and the rapidity of its production. If the collateral venous flow is sufficient, no serious results will follow, because new channels are speedily opened up to replace those which have been blocked. On the other hand, if some of the larger trunks or the main vein from an organ or a limb be obstructed and the anastomosing channels insufficient, serious derangements in nutrition take place. Examples of such main veins are the renal, the ophthalmic, the pulmonary, and the external iliac. The immediate effects will vary with the suddenness and completeness of the obstruction ; for, if it occurs suddenly, and especially if it be complete, considerable changes may take place before the collateral return can be established ; whereas, if it occurs slowly, the likelihood of a satisfactory collateral flow being established is greatly increased. Thus, in some cases of obstruction slowly produced by the growth of tumours, large venous channels may become entirely blocked without producing any serious results in the circulation. The portal vein may become wholly obstructed, and yet the blood may find its way by collateral channels into the systemic veins in such a quantity that, during life, no evidence of the obstruction may be detected. The degree of obstruction is of necessity an important factor ; for, when the lumen of a vein becomes considerably narrowed from any cause, thrombosis is liable to occur. The thrombus causes a complete block in the blood-flow, and may produce acute venous engorgement. Minute hæmorrhages are common, and larger hæmorrhages may occur from engorged vessels on the surface of the brain, in the spleen, the kidneys or the mesentery. If the obstruction is gradually produced and of long standing, the collateral veins become distended and varicose. In cirrhosis of the liver, the small branches of the portal vein within the liver are narrowed or blocked and, as a result, such distension and varicosity are seen in the tributary veins at the cardiac orifice of the stomach and at the lower end of the rectum, *i.e.*, where there is anastomosis between the radicles of the portal and systemic vascular systems : and in the epigastric veins, if the vena cava is obstructed by pressure or by thrombosis. Local venous congestion is best studied experimentally, by ligature of either a superficial vein, or of, say, the renal or the splenic vein. Immediately following upon ligature, there is distension and engorgement of all the minute veins and capillaries of the area to which the ligatured vein belongs. The area, if superficial, becomes swollen, livid, cold and numb. The distended capillaries may rupture, especially those which are poorly supported, and larger or smaller hæmorrhages may cause further swelling and discoloration of the part. Ligature of the **whole** renal vein causes marked engorgement throughout the kidney, with numerous hæmorrhages from rupture of smaller vessels. If only a **tributary** of the vein is ligatured, the engorgement and hæmorrhages are confined mainly to the special area which this particular tributary drains, but there is also a certain amount of engorgement in other areas. This latter soon passes off, and is possibly brought about fortuitously by interference with the other tributaries of the vein during the operative procedure. In the engorged area, the hæmorrhages are most liable to take place in the glomerular capsules and between the tubules in the boundary zone. They occur almost immediately after the ligature has been applied, but they become still more marked some hours later. This late hæmorrhage is due to the occurrence of degenerative changes in the walls of the capillary channels, which render them more liable to rupture. The degeneration is caused by the impaired nutrition brought about by the ligature. In disease, such hæmorrhages are an important, though not a common, result of acute congestion. They occur, as might be expected, in the case of vessels the walls of which are thin and feebly supported. In thrombosis of the ophthalmic vein, hæmorrhages are produced in the retina; hæmorrhages in the lung occur as a result of thrombosis of tributaries of the pulmonary veins; and hæmorrhage into the pia-mater over the vertex of the brain is sometimes observed as a result of sudden thrombosis of the superior sagittal sinus. The hæmorrhages are more likely to occur if there has been previous damage to the vascular endothelium by toxic or chemical substances, which may also have played some part in causing the obstruction. The distension of the veins of the part soon causes swelling, which becomes more marked at a later period, and is then due to an accumulation of transuded lymph in the tissue (*see* Œdema or Dropsy, p. 179).

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[1] From Greek, *ἴσχω, ischō,* a form of *ἔχω, echō,* meaning I check, stay, stop : and *αἷμα,* ***haima,*** blood : *Cf. ἴσχ-αιμος, isch-aimos,* a styptic which stops bleeding.

[2] " Chapters in Pathology," by W. S. Greenfield and George Lyon, Edinburgh, 1905, p. 53.

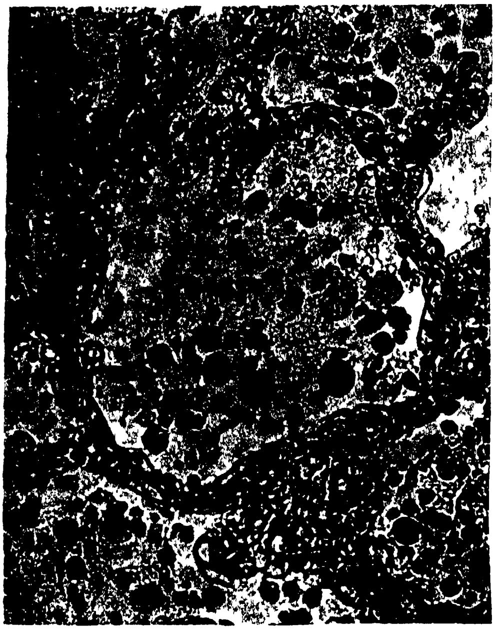

Fig. 69. Lung, showing varicosity and thickening of alveolar capillaries, in chronic venous congestion. × 200.

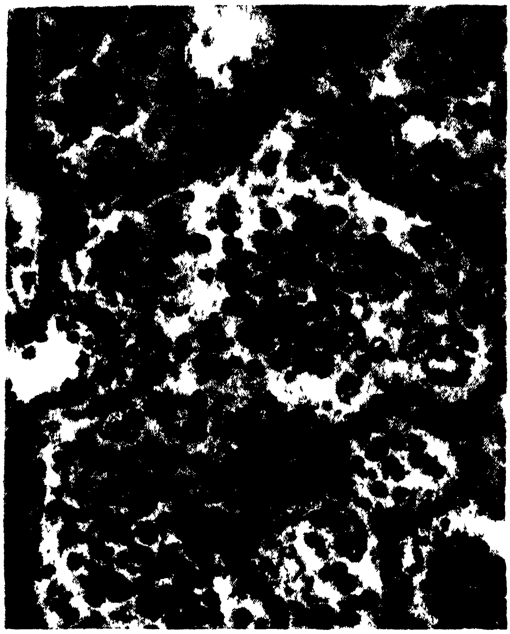

Fig. 70. Lung, chronic venous congestion. Note thickening of alveolar-walls, blood-corpuscles and pigmented catarrhal (heart-failure) cells in the alveoli (*cf.* p. 520). × 175.

General Venous Congestion. The causes of this condition are found usually in diseases of the heart or lungs, the most important of these being disease of the mitral valve (p. 459). If this valve becomes incompetent or its orifice stenosed, blood will tend to accumulate in the left auricle (atrium), free exit from the pulmonary veins will be hindered and the whole vascular system of the lungs will become engorged. The right ventricle cannot empty itself completely, because of the increased pressure in the pulmonary vessels, and the right auricle (atrium) becomes distended with venous blood, and this distension extends back into the great veins which enter it. Venous return is thus hindered, and a general distension of the systemic venous system results. The right heart becomes hypertrophied (Fig. 260, p. 460) in its attempt to overcome the resistance in the vessels of the lung, and to a certain extent, especially if the mitral valve is only stenosed and not incompetent, this hypertrophy may be able to compensate for the circulatory disturbance in the lungs and reduce its effects to a minimum. The hypertrophy of the left auricle, which results from the mitral stenosis, will exert during systole a certain amount of "backward pressure" on the blood in the pulmonary veins—especially if the left auricle is kept full of blood, as is the case in regurgitation, brought about by incompetence of the mitral valve. The result, in such cases, is the production of **chronic venous congestion** in the **lungs.** Of the systemic veins, the hepatic, splenic, and renal are most affected. In such cases, the **liver** always shows chronic venous congestion in a pronounced degree (Figs. 71 and 72). This is due to the direct and close connection between the hepatic veins and the inferior vena cava, aided by the low pressure in the portal veins and by the comparative absence of valves in the hepatic veins. The wide and open network of sinuses in the **spleen,** its circulatory relationship with the liver, and the length and tortuosity of the main splenic vein explain the readiness with which venous engorgement takes place in this organ (Fig. 73). The **kidneys** tend to show chronic venous congestion, owing probably to the relatively large size of their veins, as well as to the complexity of the arterial circulation of these organs. Chronic venous congestion may also result from fibrosis of the lung, emphysema, or pressure on the portal vein, such as occurs in cirrhosis of the liver or pressure on the inferior vena cava at its upper part. The degree of congestion varies considerably in different cases. This variation is as a rule dependent on the presence or absence of factors which act as accessory aids or hindrances to the venous return. Of these the principal is gravity. In addition, however, the position of the vessels, the condition of their walls, and the nutrition of the general muscular system of the body must be considered. If the vessels are poorly supported, and if their walls, and especially their muscular coats, are degenerated, dilatation, and also a varying degree of elongation, are liable to occur. Muscular movement is an important factor in aiding the flow of blood through the veins, and hence the value of moderate

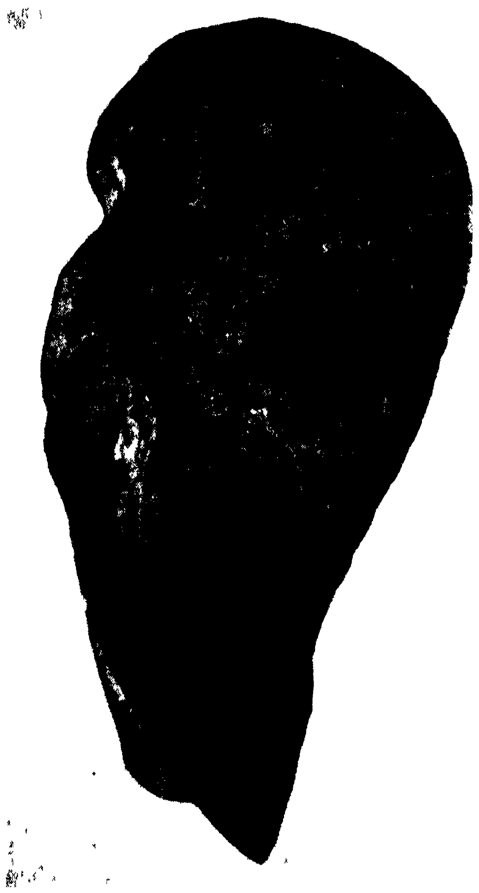

FIG. 71. Liver, chronic venous congestion showing dilated central veins surrounded by dark zones of engorged capillaries. Note also the single large dilated hepatic veins.

exercise in conditions leading to local stagnation. The driving power of the left ventricle is also a factor, because the force of the arterial, determines to a large extent that of the venous, flow. The expansion of the chest in respiration also acts by drawing the blood into the large venous trunks, and thus aiding the circulation through the lungs, so that, if the respiration is embarrassed, venous congestion is more liable to occur.

In the **stomach** and **intestine,** the mucous membrane is reddened, often brownish-red and œdematous, and minute hæmorrhages occur in both the mucous and submucous coats. Superficial to these hæmorrhages, the mucous membrane frequently becomes eroded and, in the case of the stomach, digested by the gastric juice. Thus small ulcers—hæmorrhagic erosions—are produced, and are commonly associated with gastric catarrh.

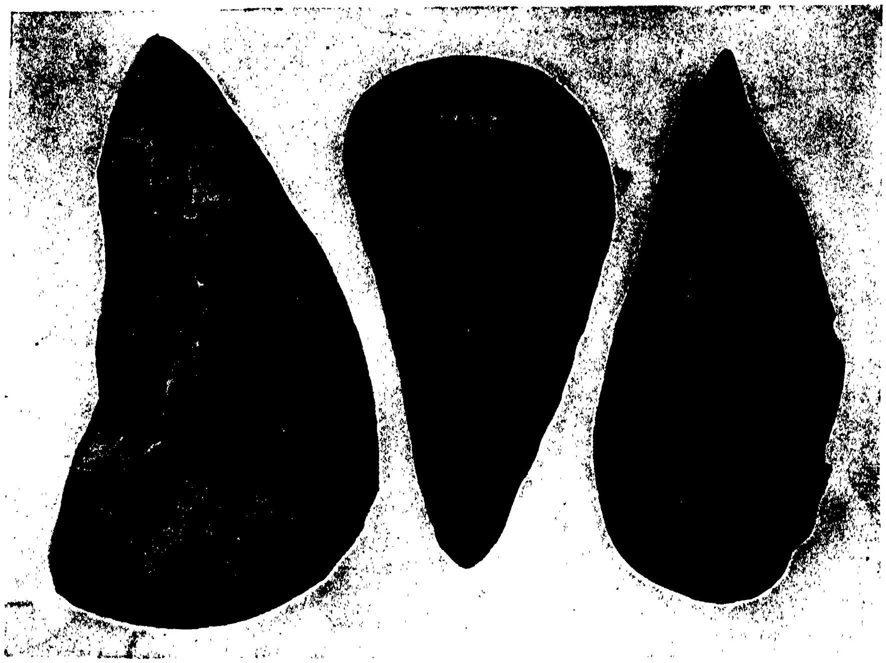

FIG. 72. Liver, chronic venous congestion. Section on left—early stage, showing dark areas corresponding to the dilated central veins surrounded by engorged capillaries. Other sections show more advanced stages with a greater extent of vascular dilatation. Note also the larger dilated hepatic veins.

The Effects of Chronic Venous Obstruction :—

On the Veins. Collateral circulation is slowly set up in the venous system, but, when once established, it almost always becomes excessive in amount by the opening up of new or, it may be, reserve vessels. Especially where the veins are not well supported, the newly opened channels, as well as those originally present, become dilated and tortuous and a condition of varicosity is produced. This is well seen in the lower limbs. The distension is always irregular, and this distension produces incompetence of the valves of the veins, which further increases the dilatation and obstruction. The action of gravity aids this to a considerable extent. In the larger veins, the walls become much thickened—usually irregularly. The muscular coat may become hypertrophied, and later fibrous, and the inner coat thickened and degenerated. The thickened and degenerated areas of the inner coat may show fatty changes and calcification. Inflammatory reactions and thrombosis are liable to occur in these damaged veins, and it is not uncommon for chronic dropsy to supervene as a result of the increased pressure and the associated vascular changes. The thickening of the smaller veins is more general and more uniform than that usually seen in the larger vessels, and confined mainly to the inner coat. In the capillaries, the thickening is in the form of fibrous laminæ just external to the endothelium. This is, in all probability, a proliferation of a delicate pre-existing layer of reticulum, which in some advanced cases becomes much thickened and fibrous. The distension of the veins and capillaries and the thickening and degeneration in their walls are seen in microscopical sections of various organs.

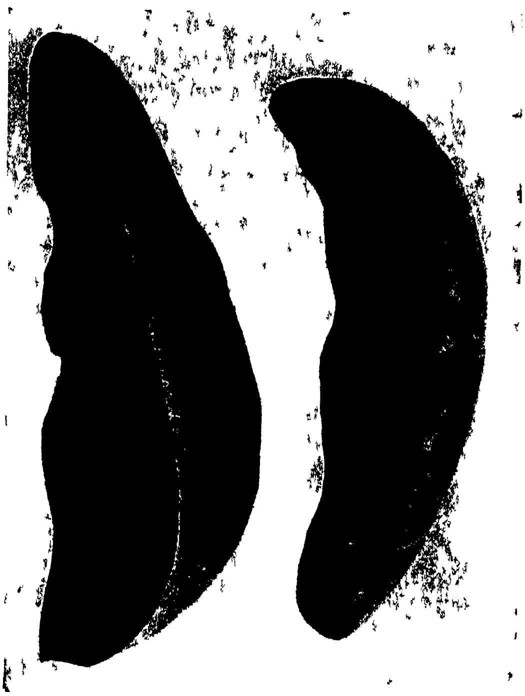

Fig. 73. Spleen, chronic venous congestion. The tissue is firm, the shape maintained and the cut edges are sharp and well defined.

In the **lungs**, all the pulmonary vessels become dilated and their walls much thickened, and hæmorrhages may occur into the pulmonary alveoli (Figs. 69 and 70). Degenerative changes, especially atheroma, sometimes advanced in degree, are commonly seen in the branches of the dilated pulmonary vessels—both veins and arteries. In the **myocardium**, the muscle, especially of the left ventricle, becomes firm and indurated, but microscopical examination shows no hypertrophy of the muscle-fibres and no fibrosis, but that the induration is due to distension of the minute veins and capillaries. A similar condition and appearance can be induced artificially by injecting the vessels with saline.

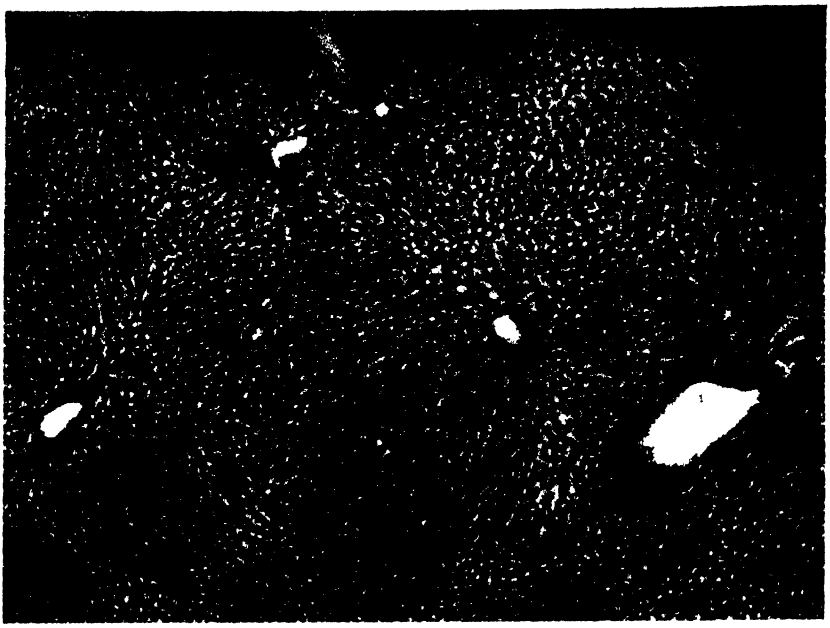

FIG. 74. Liver, early stage of chronic venous congestion, showing dilatation of central vein and capillaries, with deposit of blood-pigment. × 50.

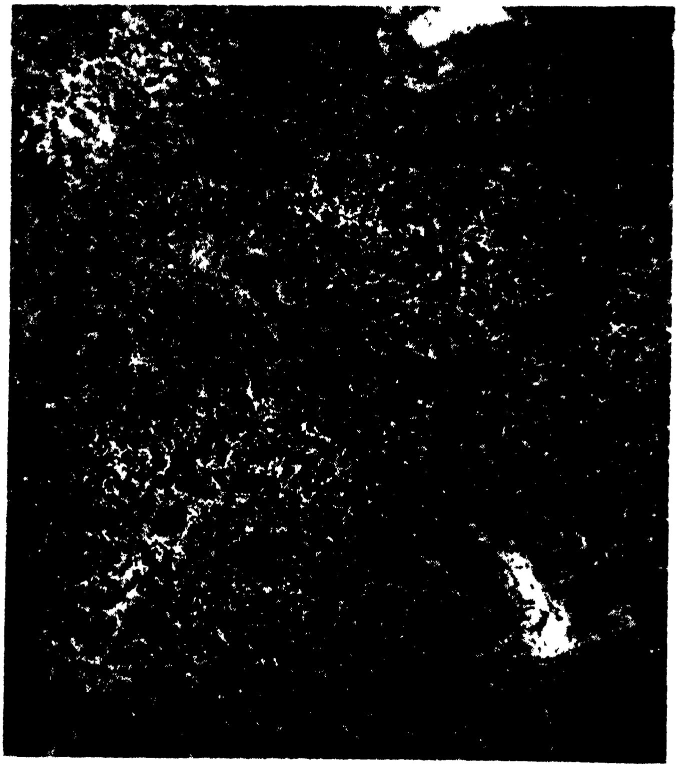

FIG. 75. Liver, chronic venous congestion—advanced stage. The cells around the portal spaces (pale areas) are comparatively healthy, but those around the central veins are atrophied or completely destroyed and replaced by dilated and congested capillaries (dark areas). × 70.

In the **spleen,** the larger veins in the trabeculæ, the venules, and the venous sinuses become greatly distended (*see* Plate X, Fig. 2, opposite p. 210, in which the congestion of the sinuses is combined with amyloid degeneration of their walls); and atrophy of the lymphoid cells of the splenic pulp, and even in some cases, though to a less degree, of the cells of the Malpighian bodies, takes place.

In the **kidney,** the distension is seen and its effects are observed especially in the venæ stellatæ, venulæ rectæ, the interlobular veins, and the glomerular capillaries in which thickening of the walls is often very evident. It is the dilated straight venules which give the characteristic dark-red striated appearance to the Malpighian pyramids in such a case (Fig. 76 and *cf.* Fig. 498, p. 856). Degenerative changes in the renal epithelium, though present, are not a conspicuous feature.

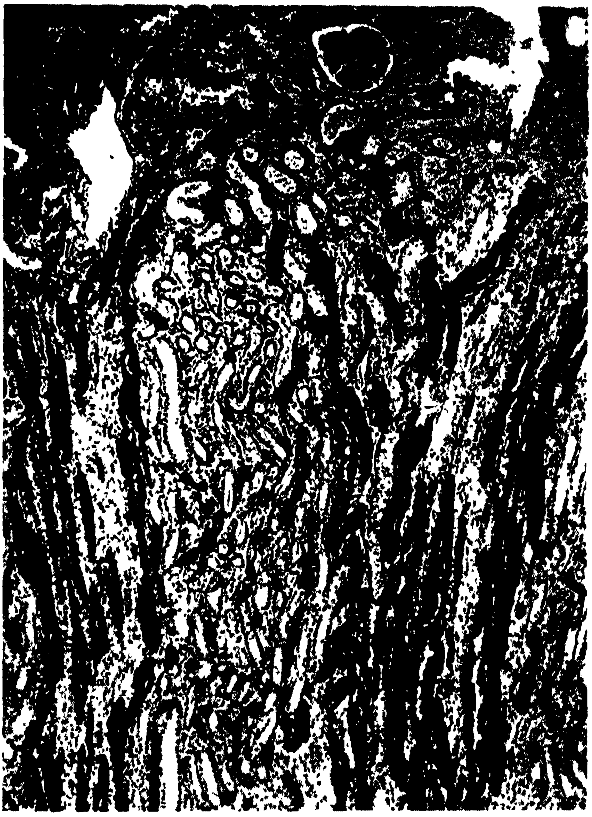

FIG. 76. Kidney, showing dark lines of chronic venous congestion in the intertubular veins and capillaries. × 60.

Hæmorrhages from the dilated veins and capillaries are apt to occur, especially in places where these are not well supported. Such hæmorrhages, as pointed out on p. 153, are frequently seen in the lung, *e.g.*, into the alveoli from the distended alveolar capillaries, or into the bronchi from the capillaries in their mucous membrane. In the kidney, also, small hæmorrhages may occur from the glomerular capillaries, and the blood may accumulate between the glomerular tuft and Bowman's capsule, small quantities being found clinically in the urine.

Organs in which chronic venous congestion is present are usually moderately enlarged, dark in colour, and firm in consistence, and generally contain a varying amount of yellowish pigment derived from the blood. The enlargement and the dark-red or purple colour are due to overfilling of the venous and capillary channels with venous blood. The dark purple colour (**cyanosis**, pp. 158 and 638) and the firm consistence have led to the use of the term "cyanotic induration" to indicate this condition. The hæmoglobin gives up an abnormally large amount of its oxygen to the tissues, and an examination of the blood will demonstrate an increased amount of reduced hæmoglobin in the capillaries and small veins. The essential factor in cyanosis, whether it results from chronic venous congestion or from some other cause, is this increase in the amount of reduced hæmoglobin. Microscopical examination shows that in certain cases there is an increase of fibrous tissue; but this is by no means common in organs in which chronic venous congestion, even in an extreme degree, exists. In the liver, in the majority of cases, fibrous overgrowth, if present, is confined almost entirely to the walls of the vessels. In the spleen, fibrous thickening is also mainly in the walls of the venules and venous sinuses, though there usually is, in addition, some thickening of the trabeculæ, but not more than might be produced by the increased strain on these structures. In the lungs, fibrous overgrowth occurs frequently in the indurated areas, and especially along the lines of the lymphatics. It occurs as an actual thickening of vessel-walls, and also in the perivascular and peribronchial connective tissue and in the interlobular septa. The increased firmness due to the fibrosis can be detected by the resistance felt on cutting into the lung at autopsy; and this feature, together with the presence of phagocytes containing blood-pigment derived from hæmorrhages into the alveoli (Figs. 69 and 70), produces the characteristic picture of brown induration. Thus the firmness of organs which have been the seat of chronic venous congestion may be due to the overfilling of venous and capillary channels, to fibrosis, or to a combination of these factors, with the proportionate effect of each varying greatly in different structures.

On the Nutrition of the Tissues. In chronic venous congestion, degenerative and destructive changes are always seen to a greater or less degree, particularly in the more highly-functioning cells such as those of the liver (p. 199). These changes are due in part to pressure upon them by the distended capillaries and veins, but the main factor is defective nutrition resulting from a deficiency of oxygen in the almost stagnant blood. The oxygen available for the nutrition of the tissues is that which is in solution in the plasma, that is, the oxygen which is dissociated from the oxyhæmoglobin within the red blood-corpuscles, and therefore free. In venous blood, the oxygen-saturation—the oxygen combined with the hæmoglobin—is from 20 to 30 per cent. less than in arterial blood, and, in passively congested capillaries, the diminution in saturation is greater and the free oxygen available for nutrition must therefore be correspondingly much lessened in amount. It follows that the prolonged deficiency of oxygen in chronic venous congestion will cause serious impairment of the nutrition of the tissues, and it seems probable that the fatty and other degenerative changes, which occur first at the centre of the lobules of the liver and gradually extend to the periphery, are due to this condition. The diminished rate of flow of the blood means the inadequate supply of nutritive substances and salts and the inadequate removal of waste products, with resulting injury to the cells. The relative individual share in this damage due to each of these agents it is not possible to determine. In the skin over varicose veins, destructive changes frequently occur, causing the so-called varicose ulcers. Mechanical pressure is here again the main factor, though alterations in nutrition and the presence of micro-organisms also play an important part.

OXYGEN-DEFICIENCY IN THE BLOOD, ANOXÆMIA or ANOXIA[1]. The oxygen-content of arterial blood, *i.e.*, its normal saturation-point, is 94–96 per cent. of its total oxygen-carrying capacity, and of venous blood 65–75 per cent. The amount of this normal free oxygen-content may be interfered with in various ways. Thus, by imperfect aeration in the lungs, the oxygen-saturation of the arterial blood may be deficient (**anoxic type**). A diminution in the total amount of hæmoglobin in the blood (**anæmic type**) will lessen its oxygen-carrying capacity ; in passively-congested capillaries the oxygen-saturation of the hæmoglobin is below the normal, the oxygen in solution is diminished, and the supply to the tissues, therefore, also lessened ; and pathological changes in the tissues themselves may render them incapable of taking up or utilising even the normal amount of oxygen.

Anoxic Type. In this type, the oxygen-saturation of the arterial blood is lessened and in consequence there will be a diminution in the quantity of dissociated oxygen in the plasma and therefore a diminished supply for the nutrition of the tissues. In order to compensate for this lessened supply, additional oxygen may be separated from the oxyhæmoglobin of the blood, and thus a further unsaturation of the arterial blood will take place. This anoxic condition is due usually to imperfect aeration in the lungs as a result of diseases such as pneumonia, emphysema, atelectasis neonatorum (p. 522), collapse, fibrosis, etc., in which the oxygen-supply-area is considerably lessened, and it may also occur in the later stages of cardiac disease with œdema of the lungs. The anoxæmia found at high altitudes is due to the diminished supply of oxygen from the rarefied air and not necessarily to any pathological condition in the lungs or blood. (*See* note *re* Aviation at high altitudes, p. 146.)

Anæmic Type. In this type, a considerable diminution in the amount of available or functioning hæmoglobin, and therefore a lessened capacity for carrying oxygen to the tissues, is found ; but there is no diminution in the oxygen-saturation of the arterial blood. On account of the diminution in the amount of oxyhæmoglobin in the capillaries, the oxygen-supply to the tissues is lessened. This type is found in Addisonian and other forms of anæmia. It occurs also in cases of carbon-monoxide poisoning and methæmoglobinæmia ; and in these, though the total amount of hæmoglobin is not diminished, a considerable proportion has been so altered chemically that it is rendered incapable of carrying oxygen.

Stagnant or Congestive Type. When cardiac compensation begins to fail, the resulting venous congestion is of this type and, though the oxygen-saturation of the arterial blood may be normal, a diminished oxygen-saturation occurs within the congested capillaries. The oxygen in solution in the plasma may thus be considerably lessened in amount, with a resulting venous unsaturation. This type of anoxæmia becomes pronounced in the later stages when cardiac compensation is failing, hypertrophy is giving way to dilatation, and œdema is supervening. In such cases, arterial saturation may fall below normal and a combination of stagnant and anoxic forms arise. General chronic venous congestion due to cardiac disease may exist without evidence of anoxæmia.

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[1] Strictly speaking, the word " anoxia " etymologically would mean " *lack of acid* " in the blood or elsewhere—*not* " lack of oxygen," the latter being the gas which " generates acid " (Greek ὀξύς, *oxus* or *oxys*, sharp, hence " sour " or " acid "). Contractions such as " anoxæmia " for " anoxygenæmia " are, however, in common use, and, on the analogy of words like " oxyhæmoglobin," are convenient though elliptical.

If, in congenital heart-disease with pulmonary stenosis, there is an imperfect ventricular septum, part of the blood from the right ventricle mixes with the arterial blood and passes directly to the aorta. In such cases, the degree of unsaturation of the arterial blood will be increased, and, in addition to the oxygen-deficiency of venous congestion, there will be a deficiency due to the imperfect aeration of the blood.

Histotoxic Anoxia. In this condition, the blood is normal in regard to oxygen-saturation, but the tissues, because of some pathological condition which is not fully understood, are unable to take up sufficient oxygen from the blood. This histotoxic form is observed in cases of alcoholic and cyanide poisoning.

Long-standing anoxæmia must have some degenerative effect on the tissues, and the fatty and necrotic changes which are seen in the liver, especially in the areas around the central veins of the lobules in long-standing chronic venous congestion, are almost certainly due in large part to oxygen-starvation; and the increased permeability of the capillaries in venous engorgement with associated œdema may be due to the impaired nutrition of the vascular endothelial cells resulting from the diminished oxygen-supply.

CYANOSIS. This condition is characterised by a bluish colour of the skin, mucous membranes, and not infrequently also of the internal organs. Over the surface of the body it may be more or less generalised, or it may be localised to the lips, nose, ears, cheeks, hands and feet. It is associated with anoxæmia (p. 157), but mere diminution or deficiency of oxyhæmoglobin, sometimes described as "oxygen-unsaturation of the blood," does not necessarily of itself produce cyanosis. Thus, in some forms of severe anæmia, the "oxygen-unsaturation" of the venous blood may be extreme and yet cyanosis not be produced; whilst in chronic venous congestion with definite cyanosis the "oxygen-unsaturation" may be less in degree. For the occurrence of cyanosis, the presence in the blood of a certain minimal amount of reduced hæmoglobin seems essential.

The causes of the condition may be classified thus :—

1. Anoxic, where there is imperfect oxygenation of the blood, with the presence of a certain amount of reduced hæmoglobin (pp. 157–8).

2. Admixture of venous with arterial blood in some congenital abnormalities of the heart (p. 446 *et seq.*).

3. Polycythæmia in its various forms (p. 638 *et seq.*).

4. Poisons causing alteration in the composition and colour of the hæmoglobin (p. 596).

1. **Anoxic.** Reference has been made (p. 157) to the various conditions

which cause an incomplete oxygenation or aeration of the blood in the lungs. These may act by causing a diminution of the aerating surface, a low oxygen-pressure in the alveoli because of the shallow breathing or other respiratory embarrassment, a reduced arterial blood-supply as in emphysema and various forms of cardiac failure, or a reduced entrance of air as in asthma and other types of spasmodic or permanent tracheal and bronchial obstruction. This anoxic variety of cyanosis is a common sequel of some forms of chronic venous congestion and especially that resulting from disease of the mitral valve. The widespread dilatation of the capillaries and the diminished rate of flow produce an increased proportion of reduced hæmoglobin in the blood. Within limits, exposure to cold, the chilling of an area, or a rise of venous pressure from local obstruction, will slow down the local rate of blood-flow in the capillaries of that area, and local cyanosis results.

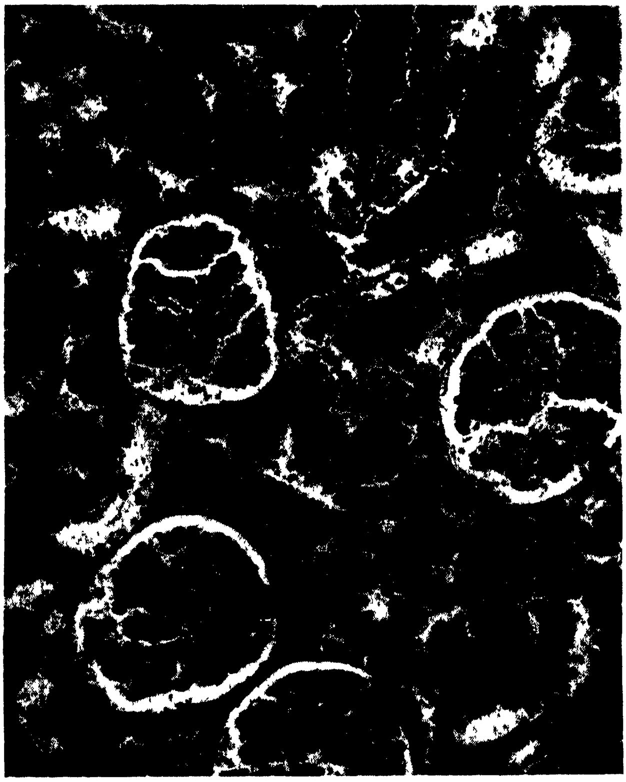

FIG. 77. Cortex of kidney, chronic venous congestion, showing dilated intertubular and glomerular vessels. The blood in the dilated vessels shows black in the photograph. × 110.

2. **In congenital heart-disease** (pp. 446–7), the cyanosis is due most commonly to an abnormal communication between the right and left sides of the heart through a patent foramen ovale, or between the pulmonary artery and aorta by a patent ductus arteriosus or an incomplete interventricular septum.

3. **Polycythæmia.** In the primary varieties of polycythæmia (*see* p. 638 *et seq.*) there is cyanosis. In these conditions, besides the increase in the number of the red corpuscles, up to 8,000,000 per c.mm. or more, and an almost corresponding increase in the total amount of hæmoglobin, perhaps even to

160 per cent., giving the blood the capacity of forming a much larger amount of reduced hæmoglobin than normal, there is also increased viscosity of the blood which slows the stream by the increased frictional resistance. Reference has already been made to the low oxygen-tension in the alveoli of the lung leading to a deficient oxygen-saturation of the arterial blood as a cause of cyanosis. This accounts to some extent for the cyanosis which occurs in individuals living at a high altitude, in whom there is a secondary polycythæmia or erythrocytosis (p. 638). This condition may be considered as compensatory and brought about by the diminished oxygen-tension in the atmosphere. It is also noteworthy that, in congenital heart-disease, polycythæmia is present, accompanied by increased viscosity of the blood. The flow through the capillaries is slowed and the actual total amount of hæmoglobin in its reduced form is increased.

4. **Poisoning.** Various compounds of hæmoglobin may be produced by the action of certain poisons or may be formed in some pathological conditions, and, where these compounds are of darker colour than normal hæmoglobin, a condition resembling cyanosis is produced, *e.g.*, by methæmoglobin or sulphæmoglobin in enterogenous cyanosis, or in poisoning with phenacetin, acetanilide and other anilin-compounds, sulphonamide-P and allied substances (" prontosil," etc.), trional and sulphonal, potassium chlorate, T.N.T. and its relatives, etc. (p. 596). Carboxyhæmoglobin, which is formed in carbon-monoxide poisoning, is a bright carmine-red and therefore its presence does not simulate cyanosis. On the contrary, when death has been due to carbon-monoxide asphyxia, the body has a peculiarly pink, life-like appearance. The presence of these abnormal pigments in the blood can be detected by their spectroscopic absorption-bands.

HYPOSTATIC CONGESTION. This term is used for a condition in which certain dependent regions of the body, particularly the bases of the lungs, become engorged with blood and œdematous, and is frequently associated with collapse and patches of consolidation, bronchopneumonic in type—the term **hypostatic pneumonia** being applied to the condition. These changes are seen in debilitating diseases of all kinds, especially where the patient is confined to bed. The production of such lesions is aided by gravity, but there are many other factors at work. In debilitated patients, deficient expansion of the lungs, combined with weakened action of the respiratory muscles, is an unavoidable consequence of the recumbent position, and congestion and collapse are liable to occur. The collapse is aggravated by the accumulation of catarrhal secretions, which gravitate to the lower lobes of the lungs, especially if bronchitis is present. Distension of the stomach and intestine may interfere with the action of the diaphragm. The congestion is intensified by a weak circulation in cases where the heart is acting feebly. All these agencies play their part in the production of the condition.

THROMBOSIS

Under the term **thrombosis** are included all forms of coagulation of the blood occurring, during life, in the heart or vessels, and in cavities and dilatations connected with these, the resulting mass being known as a **thrombus**.

Mechanism of Coagulation. Coagulation of the blood, whether extravascular or intravascular, is due to the formation of the insoluble protein, fibrin, by the interaction of the enzyme, thrombin, with soluble fibrinogen of the plasma. Thrombin or thrombase is not present in the circulating blood, but is formed from an inactive precursor—prothrombin (prothrombase)—in the presence of ionised calcium and thromboplastin. Prothrombin and ionised calcium are present in the blood normally. Thromboplastin[1] is present in and is liberated from the blood-platelets, leucocytes and tissue-cells when these have been disintegrated or damaged. Tissue-extracts alone, freed as far as possible from calcium, will in a few hours bring about the conversion of prothrombin into thrombin, but the addition of minute traces of calcium greatly accelerates the reaction. In the process of clotting, the blood-platelets disintegrate and liberate thromboplastin, and this, in the presence of ionised calcium, is believed to activate the prothrombin of the plasma into thrombin which, in turn, converts the fibrinogen of the blood into insoluble fibrin. Thromboplastin is probably also liberated from damaged tissue-cells, *e.g.*, of the heart and vessels. This reaction may be represented as follows :—

$$\underset{\text{(In plasma)}}{\text{Prothrombin}} + \underset{\text{(In platelets and cells)}}{\text{Thromboplastin}} + \underset{\text{(In plasma)}}{\text{Calcium-Ions}} = \text{Thrombin.}$$

$$\text{Thrombin} + \text{Fibrinogen} = \text{Fibrin (Clot).}$$

Hypothrombinæmia. Experimental work by Henrik Dam and Schönheyder (1936) of Copenhagen, Dam and Glavid (1938), Scarborough (1939) and others, has shown that, in certain of the hæmorrhagic diseases of infants (pp. 587–8) and in obstructive jaundice in adults, a **deficiency in the prothrombin-content** of the plasma occurs, and is probably responsible for the increased tendency to bleeding in these disorders. This deficiency in prothrombin may be due to any of the factors mentioned on p. 442, including an **insufficient supply of vitamin K** in the diet or the inefficient absorption of it from the intestine owing to the absence of bile-salts. The administration of vitamin K ("**K**" is the initial letter of the Danish word "**K**oagulation") by the mouth or intramuscularly in hæmorrhagic diseases of this type raises the prothrombin-level and thus shortens the coagulation-time ; and in obstructive jaundice the tendency to hæmorrhage is corrected if the vitamin K is given in association with bile or bile-salts. The **prothrombin-content** of the blood can be determined by estimating the **coagulation-** or **prothrombin-time** in the oxalated plasma in the presence of added excess of thromboplastin (in the form of an emulsion of desiccated brain containing it) "re-calcifying" with calcium chloride and incubating at blood-temperature until coagulation takes place. The **prothrombin-index** is the ratio between the normal coagulation-time and that of the plasma from the patient under observation.

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[1] **Thromboplastin,** or, as it has been named by various authors, thrombokinase, thrombozyme, thromboplastic substance, cytozyme, or zymoplasm, is, as stated above, present in blood-platelets, leucocytes and tissue-cells. It can be extracted by water or saline from lung, brain, heart and other organs and tissues. It is probably of the nature of an enzyme, but its chemical constitution has not yet been definitely determined.

Under normal circumstances, *i.e.*, with healthy vessels, a normal rate of blood-flow, and with blood in a normal condition, no coagulation takes place within the vessels or the heart; but, if this balance is upset, thrombosis may occur. If the vessel-wall is injured, or if irregularities are produced on its inner surface by disease, the blood-flow is impeded, and the blood-platelets tend to adhere to, and accumulate on, the damaged parts. Mere slowing of the blood-stream from any cause in undamaged vessels is claimed by some authors to give rise to coagulation. Whether this view is accepted or not, the slowing is an important factor. In the majority if not in all cases of thrombosis, some damage to the inner lining of the vessel is present—produced, it may be, by mechanical injury, bacteria, toxins, metabolic poisons, etc., though the damage may be so slight as to be overlooked. In some cases, it may be difficult to explain the reason for the formation of a thrombus and, with our present methods of investigation, perhaps not possible to demonstrate any pathological cause, yet there is no experimental evidence that thrombosis can be produced without damage to the wall of the vessel in which the thrombus has been formed. W. H. Howell (1916) and his co-worker, Emmett Holt[1] (1918–19), of Johns Hopkins University, suggest that the fluidity of the blood (as well as of other body-fluids, including the synovial fluids of joints) is maintained by the presence of two natural or physiological **anti-coagulant** substances in them: **pro-antithrombin** (the mother-substance of antithrombin): and **heparin** (a tissue-extract obtained most readily and abundantly from liver, lung, spleen and skeletal muscle). For thrombosis of the blood to take place, there must be the possibility of a reaction between **thrombin** and **fibrinogen**—the thrombin being formed from the normally-present prothrombin under the activating influence of a thromboplastic substance derived most usually from blood-platelets. Howell, however, states that the presence of **calcium** is also necessary for the activation of prothrombin into thrombin. Therefore, in view of the fact that the essential factors for the production of coagulation—**prothrombin**: **fibrinogen**: and **calcium-salts**—are already normally present in the plasma, Howell assumes that coagulation is, in ordinary circumstances, *prevented* by some substance which *protects* the prothrombin from the action of the calcium. This substance, because it was first obtained from liver, he has called "heparin." When damage to the vessel-wall or surrounding tissues likely to lead to the production of thrombosis has taken place, the platelet- or tissue-content liberated neutralises this natural anti-coagulant (heparin), and thus—depriving the prothrombin of its protective influence—renders it susceptible to activation by the calcium, with its resulting transformation into **thrombin**. There is abundant evidence, both experimental and clinical, that the addition of heparin to the blood hinders or prevents coagulation. Jorpes, and his colleagues, Holmgren and Wilander,[2] have brought forward evidence which goes far to prove that, in the animal body, heparin is formed and secreted by the widespread system of **basiphil cells** (usually known as the "mast-cells" of Ehrlich),[1] the characteristic metachromatic granules of which are stated by Jorpes to consist of a poly-ester of sulphuric acid of high molecular weight and closely resembling heparin itself in chemical composition. The presence of a few of these basiphil cells in the blood—presumably more or less an "overflow-phenomenon"—has long been recognised, and also their presence in varying numbers in many organs and tissues; but not until recently have any suggestions been made as to their functions. They are found especially in the immediate neighbourhood of the blood-vessels, as well as in the walls of these (Fig. 360A, p. 599), and in the connective-tissue framework of the lungs, liver, etc.; and it thus seems reasonable to assume that they are directly concerned with the **production of heparin** which these Swedish observers and their colleague, Bergström, believe to be "mucoitin-polysulphuric acid," which is said to be "the strongest known organic acid." It has now been produced commercially, and can be used both prophylactically and therapeutically, *e.g.*, for the prevention of post-operative thrombosis and the consequent danger of infarction of the lung: and for checking the extension of coronary thrombosis, thrombosis of the central vein of the retina, or thrombosis in cerebral vessels.

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[1] W. H. Howell and Emmett Holt, "Two New Factors in Blood Coagulation—Heparin and Pro-antithrombin," *American Journal of Physiology,*" 1918–19, **47**, 328. See also "Heparin: Its Chemistry, Physiology and Application in Medicine," by J. Erik Jorpes, Stockholm, Oxford University Press, 1939; and W. H. Howell's "Textbook of Physiology," 14th Edition, Philadelphia and London, 1940, p. 459.

[2] Hjalmar Holmgren and Olof Wilander, "Beitrag zur Kenntniss der Chemie und Funktion der Ehrlichschen Mastzellen," *Zeitschrift für mikroscopisch-anatomische Forschung,* 1937, **42**, 242.

Fibrin appears as a structureless solid of highly variable morphology—fine mossy fibrillæ, coarser rods and "shepherds' crooks," radiating stellate figures and coarser granular masses. The fibrillar and rod-like forms have a refractive index differing from tissue-fibrils, so that they exhibit, under the microscope, a glistening appearance in a focal plane at which connective-tissue fibrils are dark. Fibrin is stained a very pale bluish-pink with hæmatoxylin and eosin, but readily becomes basiphilic through the absorption of diffusing chromatin. It can be stained selectively by the Weigert-Gram method.

Fibrin is an essential component of all blood-clots, of which the following varieties are recognised: (*a*) **red** clots, also called "**currant-jelly**" clots, in which there are many red cells, because no segregation had taken place before clotting; (*b*) **white** clots, largely lacking in both red and white cells and composed almost entirely of fibrin and platelets; (*c*) **yellow** clots, which are rich in white blood-cells and are found in the clotting of leukæmic blood and in regions in which leucocytes have been increased by segregation; and (*d*) **mixed** and **laminated** clots, which show a combination of various types.

Varieties of Thrombi. Thrombi are usually described as **red** and **pale** or **white,** which differ, not only in colour, but also in their mode of formation.

Red Thrombi. These are formed in cases where there is rapid coagulation of the blood from any cause; and, in their method of formation, they are, for all practical purposes, identical with the clotting which takes place outside the body. These clots are formed in the heart just before death, when the circulation is failing: or immediately after death: or in the blood-vessels, usually as an extension of a pale thrombus, when there has been a sudden arrest of the blood-flow. They are generally voluminous; may completely fill the chamber of the heart or the lumen of the vessel; and are composed of red corpuscles, disintegrated blood-platelets, entangled leucocytes and fibrin-threads which are arranged very irregularly.

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[1] That this term "mast-cell" is unfortunate and inappropriate, in that it implies a non-existent degenerative condition of the cell, is explained in the footnote on p. 623, in which connection *see also* pp. 27 and 599.

Pale Thrombi. In speaking of pale thrombi, it must be clearly understood that we refer to those which are pale from the beginning, and which have been slowly formed ; and we must distinguish between these and the red thrombus which, by decolorisation, has become pale some time after its formation.

The true " pale " thrombus is usually of an opaque, dull-white colour, firm in consistence, and often more or less adherent to the wall of the vessel or to the endocardium. These pale thrombi are primarily and essentially composed of disintegrated blood-platelets.

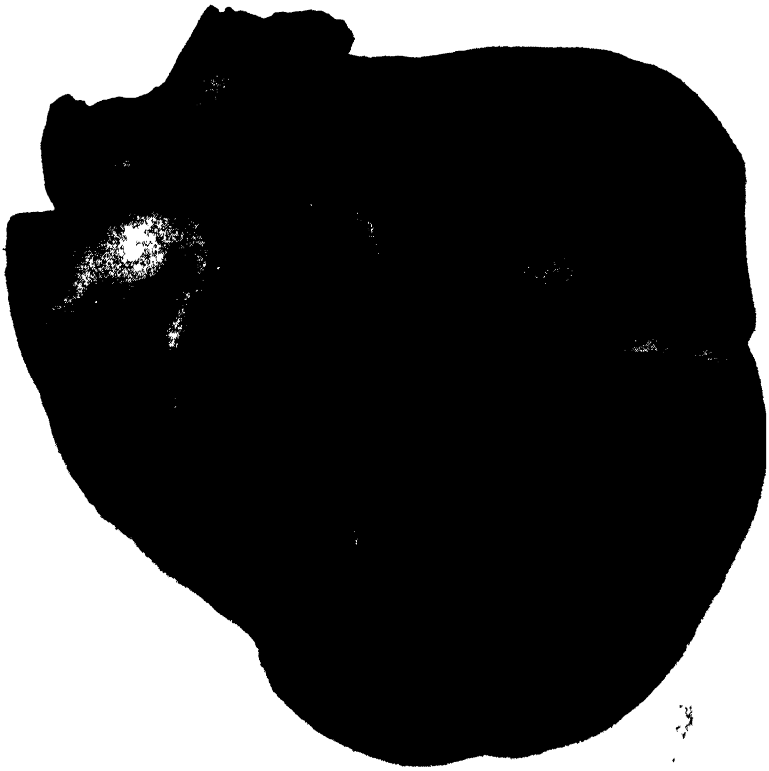

FIG. 78. Heart. Large ball-thrombus which had formed in the left auricle of female patient aged 42, who had suffered from mitral stenosis.

The pale, often yellowish-coloured, translucent, soft clot, sometimes described as "**chicken-fat**" clot, seen very frequently in the heart at a post-mortem examination, is formed by coagulation of the serum after a partial separation of the erythrocytes. This clot, which is not a thrombus, is composed largely of fibrin. Some authors describe these clots as **fibrinous** or **lard-like** clots, and limit the use of the term "**chicken-fat clot**" to those which are rich in white blood-cells and are seen in the clotting of leukæmic blood, and in regions in which leucocytes have accumulated by segregation.

If a vessel be compressed or twisted with artery-forceps in such a way that the endothelium is injured, or if the endothelium is damaged by the diathermy-needle or by chemical means, and at the same time the blood-flow retarded, the blood-platelets accumulate upon the injured area and become fused together, or "conglutinate." This process is the basis of thrombus-formation (*see* p. 162). The leucocytes and the red blood-corpuscles play an entirely passive part, and merely become entangled in the developing thrombus. In some vessels the thrombus consists wholly of fused blood-platelets, and in others, where the thrombosis is well advanced, the leucocytes can be seen practically unaltered. These observations were made on numerous specimens which we were enabled to examine through the kindness of the late Professor Greenfield of Edinburgh, and we have fully confirmed the observations which he himself made on this subject.

The characters and situations of thrombi, and the conditions under which they occur, are most conveniently described if the three important sites—the heart, the veins, and the arteries—are treated separately.

The Heart. Clotting of blood in the various chambers of the heart is usual after death, and it is important to distinguish between these post-mortem clots and thrombi formed before death, or during the period of dying. The post-mortem clots are either dark in colour, or they may be combined with pale or yellowish coagulum. The pale portion is most commonly found lying on the surface of the dark clot, and is due, as already stated, to coagulation of the plasma from which the red blood-corpuscles have been separated by gravity. The post-mortem clots, of whatever colour, are soft and easily broken down. The ante-mortem thrombi are pale in colour, opaque, tough and stringy, and may be adherent to or entangled in the muscular columns of the heart-wall, especially on the right side. In some cases they lie free in the cavities of the heart as "**ball-thrombi**" (Fig. 78). "**Intermediate**" or "**agony**" **clots** which are formed during the period of gradual heart-failure are sometimes difficult to differentiate from true ante-mortem thrombi. They are frequently attached to some ante-mortem thrombus in the right auricular appendix (auricle), and tend to spread downwards through the tricuspid orifice towards the apex of the right ventricle, where they are frequently entangled in the muscular bands. They may then pass upwards for a varying distance into the pulmonary artery. They are often well developed in fatal cases of pneumonia. These clots, on microscopical examination, are found to consist largely of fibrin-threads and entangled leucocytes. The true ante-mortem thrombi in the heart are found most commonly at sites where there is slowing of the blood-stream or where eddies form. The auricular appendices (auricles), especially the right, are by far the commonest sites. The thrombi are also found entangled in the columnæ carneæ of the ventricles, more particularly towards the apex, and are specially well seen if there has been previous damage to the heart-wall, *e.g.*, over the endocardial surface of an infarction of the heart. Ante-mortem thrombosis frequently occurs on valves which are the seat of inflammatory changes or of chronic fibroid thickenings. These so-called **vegetations** are composed almost wholly of fused blood-platelets, firmly adherent to the diseased valve. The superficial parts may be very friable, and are often crowded with micro-organisms.

Of Veins—Phlebothrombosis (*see* Fig. 79). The veins are, during life, the commonest sites of thrombosis, which results from two main causes: (*a*) slowing of the blood-stream: and (*b*) dilatation, tortuosity, and other diseased conditions of the vessels. The thrombus commences very commonly as an accumulation of blood-platelets in the pouch of one of the valves: at the junction of a tributary with a larger vein or venous sinus; or at a part of the wall which has been injured. By the gradual accretion or conglutination of platelets, the mass increases in size until it blocks the lumen. Then follow rapid coagulation and formation of red clot, which extends up and may terminate at the point of junction of the thrombosed vein with an adjoining or tributary vein. The clot may project into the lumen of the larger vein and cause obstruction. Further coagulation follows, and, in some instances, extensive and progressive thrombosis may result. Thus, thrombosis, commencing in, say, one of the superficial veins of the foot, may extend so as to fill the whole femoral vein, and may even be prolonged through the iliac veins to the inferior vena cava. In these examples of extensive thrombosis, the starting-point may have been a slight injury to the vein : or a septic focus in it, *i.e.*, a phlebitis, this leading to the production of a **thrombophlebitis**; but the spread is often due to a weakened condition of the heart's action, favoured, no doubt, by general debility, and, it may be, by some pathological condition of the blood itself. The uterine veins, and also the deep veins of the calf of the leg, may be the starting-points of very extensive areas of thrombosis. The thrombi formed in cases of general debility are called **marantic** thrombi. We believe, however, that many of these are really due to the presence in the blood of abnormal products of metabolism or toxic products of bacterial infection, which act, not merely by damaging the vascular walls, but also by causing alterations in the coagulative power of the blood. It has been shown experimentally that the injection of peptone, various tissue-extracts, and some animal poisons, *e.g.*, snake-venom, brings about coagulation. Bacterial poisons, especially those produced by growth of the pneumococcus, may also cause coagulation. The coagulating power of snake-venom has been utilised in the treatment of hæmophilia (pp. 670–1). (For thrombosis of cerebral veins and venous sinuses, *see* p. 973.)

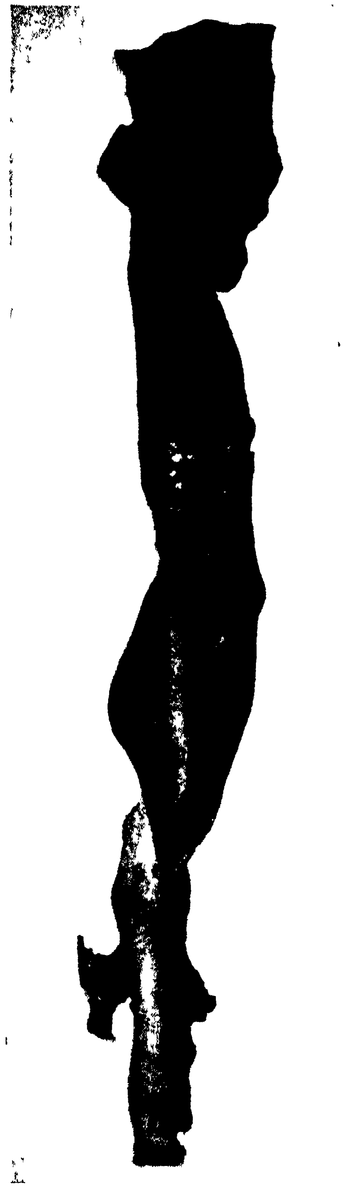

FIG. 79. Thrombosis in iliac and femoral veins. Adhesion and partial organisation of thrombus towards upper part.

Of Arteries. Local thrombosis on roughened or degenerated patches in arteries is not uncommon, but complete obstruction is rare. Where the lumen of the artery has been much narrowed, as in some cases of atheroma, the obstruction to the blood-stream may be so great that complete thrombosis occurs. This is seen sometimes in the cerebral arteries. In arteries in which there has been complete obstruction by means of an embolus, thrombosis supervenes and usually spreads to the first collateral branch. Even after ligature of an artery, the thrombus-formation may be very slight, a small, pale, conical thrombus being formed on the proximal side of the ligature. On the distal side, the clot, if present, is of the red variety. Later, the thrombus may be to a considerable extent absorbed. It may become adherent at one side, and the lumen may be patent on the other. Such thrombi adhering to the wall of the vessel are described as " parietal." **Thrombosis in aneurysms** and the formation of laminated clot are described under Diseases of Vessels (p. 496). **In surgical operations** in which the **diathermy-knife** or **needle** is used, bleeding may be minimised or even prevented by a combination of **heat-coagulation** of the tissues and the blood-vessels and their contents, together with the ensuing **thrombosis** of blood within, and **clotting** of it outside, the vessels (in connection with which, *see also* p. 1058).

Capillary thrombosis is frequently seen in inflammatory conditions, and the walls of the vessels may undergo necrosis. The thrombi are usually composed of red corpuscles and coagulated plasma, but probably, in these thrombi also, the basis is disintegrated platelets.

Subsequent Changes in a Thrombus. A thrombus, as has already been indicated, may become wholly or partially absorbed. This is brought about by fibrinolytic ferment, by hæmolysis, and by the phagocytic action of wandering macrophages. The fibrinolytic ferment produces fragmentation of the thrombus, and embolism (*see* p. 168) may result. This is called "**simple**" or **aseptic softening.** In the presence of bacteria, as in **thrombo-phlebitis purulenta,** fragmentation is more likely to occur, and this septic softening is especially liable to produce multiple emboli which may be widely distributed. Under more favourable conditions, encapsulation by fibrous tissue and organisation take place. The newly-developed blood-vessels bring about canalisation of the thrombus (*see* Repair, p. 51). The thrombus may eventually become **calcified,** leading to the formation of a " phlebolith " or " arteriolith."

ARTERIAL OBSTRUCTION

If an artery is obstructed, either partially or completely, pallor of the area supplied by the artery is produced. This local pallor, due to a defective blood-supply, is usually designated by the term **ischæmia.**[1] If the obstruction is partial, or more especially if it is temporary, only slight nutritive changes may be produced. More serious results follow from complete obstruction, and it is to these especially and to the causes of obstruction that reference will be made.

1. **Changes in the wall of the artery itself.** The lumen of the artery may become narrowed by excessive contraction of its muscular coat, or by proliferative or degenerative changes, especially in the inner coat. The contraction of the muscle may be due to excessive stimulation of the vaso-constrictor nerves ; and, though this rarely gives rise to serious nutritive disturbances, necrosis and gangrene may ensue, as in some cases of the syndrome known as " Raynaud's disease " (p. 187), in which the phenomenon of vaso-constriction is constantly repeated, a sequel which may, however, in suitable instances, be prevented by sympathetic ganglionectomy (p. 1193 *et seq.*, and Figs. 764 to 768).

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[1] For derivation and meaning of " ischæmia," *see* footnote on p. 148.

Contraction of the muscular coat of the arteries may also be produced by the direct action of electrical stimulation upon its muscle-cells, by excessive heat or cold, and also by certain poisons (*e.g.*, lead, ergot) and suprarenal extract. The prolonged administration of ergot medicinally, or by the eating of bread made from rye infected by this fungus, sometimes gives rise to serious consequences, including gangrene ; but, apart from ergotism, muscular contraction caused by these agents is not commonly sufficient of itself to bring about complete obstruction, though some of them—*e.g.*, lead—by causing prolonged partial obstruction, may be the cause of atrophy and necrosis (pp. 186, 244 and 483).

The proliferative and degenerative changes in the walls of the arteries, such as are found in atheroma or in syphilitic disease, rarely of themselves give rise to complete obstruction ; but the narrowing and the degenerative changes combined are frequent causes of thrombosis, and thus the partial obstruction may be made complete.

2. **Compression of the artery from without,** *e.g.*, by a ligature or by pressure of a tumour : or infiltration of the wall by new growth.

3. **Obstruction of the lumen of the artery.** The commonest cause of the complete arrest of the arterial supply is **obstruction of the lumen** by a locally-formed thrombus or by the carriage from a distance of a portion of a thrombus, a clot, or a foreign body such as a fragment of a tumour, which becomes impacted in an arterial branch, the process being known as **embolism,** and the impacting body as an **embolus.**

EMBOLISM

The commonest sites of origin of emboli are the heart-valves in endocarditis, more especially those of the left side, the mitral more frequently than the aortic. Sometimes portions of a thrombus in a chamber of the heart or in an artery or vein, or formed on atheromatous patches in the walls of the aorta or other large artery, become detached and give rise to emboli. The **embolus,** from whatever source it comes, is carried by the blood-stream until it reaches an artery whose diameter is less than that of the embolus, and there it becomes impacted, such impaction often occurring at the bifurcation of a vessel. The obstruction in the artery may be at once complete ; or if not, it usually soon becomes so by the occurrence of thrombosis, which may spread for a considerable distance forwards in the artery, and also backwards to the first collateral branch. After impaction, the embolus may be broken up and the smaller pieces carried further into the vessels, and thus one form of multiple embolism results. The vegetations in septic endocarditis and the infective thrombi of veins are soft and easily fragmented, and the fragments which are carried into the blood-stream contain, as a rule, pyogenic bacteria, and become impacted in the smaller vessels of the brain, spleen, kidneys and lungs and in these organs may give rise to **multiple pyæmic abscesses.** Those occurring in the lungs are usually secondary to septic thrombosis in a systemic vein.

In addition to the emboli formed from vegetations or thrombi, sometimes —though much more rarely—embolism results from the blocking of arteries **by air, by fat,** by tumour- or other cells, and by animal or vegetable parasites.

AIR-EMBOLISM. This is rare. During a surgical operation or in accidental or wilful wounds of the neck (cut-throat), when large veins in the neck, near the thorax, are opened, air may be aspirated into the heart, and occasionally death from air-embolism occurs. In such cases, air-bubbles and a frothy condition of the blood are found in the large veins near the heart, in the right auricle (atrium) and ventricle, and in the pulmonary capillaries.

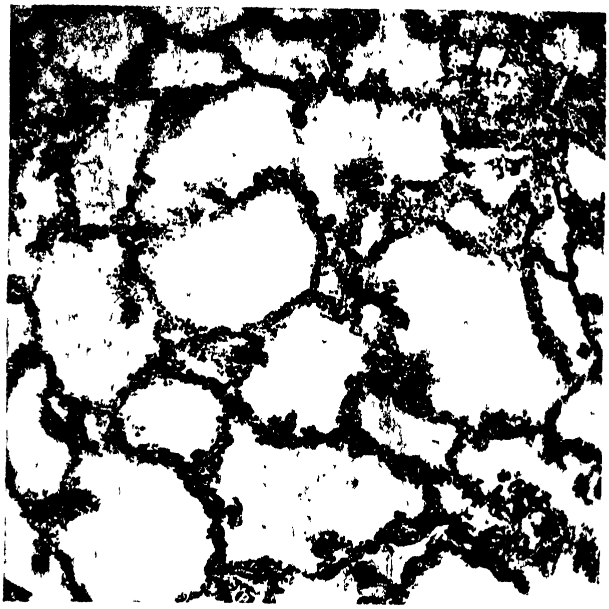
FIG. 80. Fat-embolism of lung, showing fat-globules (black) in the capillaries. Stained with osmic acid. × 60.

If animals are subjected to the action of compressed air for varying periods and quickly decompressed, bubbles of gas are liberated in the blood-vessels, heart and liver. From such experiments the main symptoms of caisson-sickness and divers' palsy are regarded as due to air-embolism (*cf.* p. 146). This conclusion is based on the facts that, during compression, a large amount of air, chiefly nitrogen, is dissolved in the blood-plasma; and, if decompression takes place too rapidly, the air escapes in the form of bubbles, which produce air- or froth- emboli in the brain, spinal cord, heart, and other organs, with resulting small infarcts.

The presence of gas-bubbles in the blood and in the viscera, *e.g.*, the liver, sometimes seen *post mortem*, is due, in the majority of instances, not to air-embolism, but to the production of gas in the body, mainly, but not always wholly, after death, by bacteria specially concerned in the processes of decomposition and in the condition of gas-gangrene (pp. 235 and 253–5).

FAT- or OIL-EMBOLISM. Globules of fat may enter the blood-stream following fractures of bones with laceration of the bone-marrow, forcible manipulation of bones in the attempt to break down adhesions, crushing injuries of bone, especially of the ribs, lacerations and contusions of adipose tissue, injuries to the liver, etc. In accident-cases, it is by no means an uncommon complication, and it has been found in from 20 to 25 per cent. in some series of cases which were investigated for its occurrence (Robb-Smith [1]). The fat gains access to the veins, is carried to the right side of the heart, and thence to the pulmonary capillaries. In advanced fatty degeneration of the liver-cells, *e.g.*, in delayed chloroform-poisoning or in phosphorus-poisoning, globules of fat are sometimes found in the capillaries of the lung, and there seems no reason to doubt that the fat has come, in the form of emboli, from the degenerated liver-cells. In fatal cases, the mechanical plugging of the vessels with fat occurs in scattered areas throughout the **lungs** [2] (*cf.* p. 537), associated with patches of emphysema, œdema, congestion and petechial hæmorrhages both in the lung-substance and under the pleura—progressing, it may be, to patchy pneumonic consolidation, and giving rise to appearances very similar to those seen in early acute septic infection of the lungs. When such appearances are found in cases of death following upon crushing injuries, the lungs should, therefore, be carefully examined for the possible presence of fat-embolism. The fat, entering the veins, may not only produce these effects in the lung itself, but may also pass through the pulmonary capillaries and become lodged in the brain, the glomeruli of the kidney and elsewhere. In the **kidney,** such fat-emboli have, as a rule, little or no obvious clinical consequences, though some of the fat may be found floating on the surface of the voided urine. In the **brain,** the characteristic lesions are pinkish areas of hyperæmia and softening, and small patches of hæmorrhage—many of them microscopic, often in the form of rings or zones of extravasated red corpuscles around capillaries and pre-capillary arterioles which have been blocked by the spherical and sausage-shaped globules of fat. Some of these small vessels also contain fibrin and leucocytes, and show perivascular demyelination of the brain-tissue around them, and varying degrees of secondary degeneration in their areas of distribution (p. 1029)—these lesions in the brain sometimes giving rise clinically to symptoms simulating those of apoplexy or subdural hæmorrhage. In addition to the changes in the brain-tissue itself, the occurrence of extensive occlusion of the vessels of the choroid plexuses by the embolic fat has been described by Dorothy Russell.[1]

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[1] "Discussion on Fat Embolism and the Brain," Section of Neurology, *Proc. Roy. Soc. Med.*, 1941, **34**, 639.

[2] The embolic fat can be demonstrated by clearing thick fresh sections of the lung in 2 per cent. potassium hydroxide solution.

EMBOLI of TUMOUR-FRAGMENTS, or of FRAGMENTS of TISSUE. Emboli consisting of fragments of tissue derived from the liver after rupture or following extreme degeneration, from the bone-marrow in leukæmia, from the placenta, or due to the presence of animal parasites, are uncommon ; but emboli of tumour-fragments which gain entrance to the circulation by erosion of the wall of an artery or a vein are of more frequent occurrence, *e.g.*, in chorionepithelioma and bronchial carcinoma. Usually these are very small, but occasionally tumour-fragments of larger size are found impacted in some of the arteries. Such larger emboli are sometimes seen in branches of the portal vein in the liver. After impaction, these tumour-cells may undergo proliferation and give rise to metastatic new growths.

The Sites of Emboli. As a rule, emboli from the valves or chambers of the heart are carried by the blood-stream, and become arrested merely because the lumen of the artery is too small to allow them to pass. Thus there seems no special reason why they should occur in one organ more than in another. Judging from records of the post-mortem room, the commonest sites are the kidney, spleen, and brain. Probably many of the other vessels, *e.g.*, those of the limbs, receive the emboli ; but the obstructed vessels are—owing to the free anastomosis present in these regions—of comparatively little importance, and no symptoms or signs follow the impaction, unless the emboli are septic. Emboli derived from veins, *e.g.*, varicose veins of the limbs or the pelvic veins, or from the right side of the heart or pulmonary artery, become impacted in the branches of the pulmonary artery ; those coming from the pulmonary veins, the left side of the heart or its valves, or from the arteries themselves, lodge in the systemic arteries ; whilst those coming from radicles of the portal system become impacted in the branches of the portal vein in the liver.

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[1] *Loc. cit.* in footnote on p. 169.

The emboli found in the pulmonary artery arise most commonly as a result of thrombosis in the right auricle (atrium), and more especially in its dilated appendix in chronic disease of the heart. The thrombus or detached fragments of it carried through the right ventricle and pulmonary artery become impacted in vessels of the lung and give rise to pulmonary apoplexy or infarction, which, when large, may cause sudden death (p. 177).

It has been already stated that, as a rule, emboli are carried with the blood-stream, and follow its normal course, but there are some exceptions :—

1. **" Crossed " or " Paradoxical " Embolism** (p. 1029). This is produced by emboli which pass from the systemic veins with the blood-stream through a patent foramen ovale into the left auricle, and so into the systemic arteries.

2. **Retrograde Embolism.** This phenomenon occurs chiefly in veins, the emboli being carried in a direction opposite to that of the blood-stream. This is usually explained as due to a temporary reflux of the blood in the vein, produced by some obstruction to the return of blood to the right heart . or from a sudden temporary increase in pressure within the larger veins of the thorax or abdomen, for example in coughing, which produces a retrograde flow of blood into the smaller tributary and anastomosing prevertebral and vertebral veins The important experimental work of Professor Batson,[1] of the University of Pennsylvania, in this connection may help to explain the mechanism of the common occurrence of metastases in the bones of the vertebral column from prostatic and mammary carcinomas as due to the retrograde embolic carriage of tumour-cells in this way (*see also* pp. 274, 915, 948, and 1144-5), as well as the analogous occurrence of metastatic abscesses from a similar backward carriage of infected emboli.

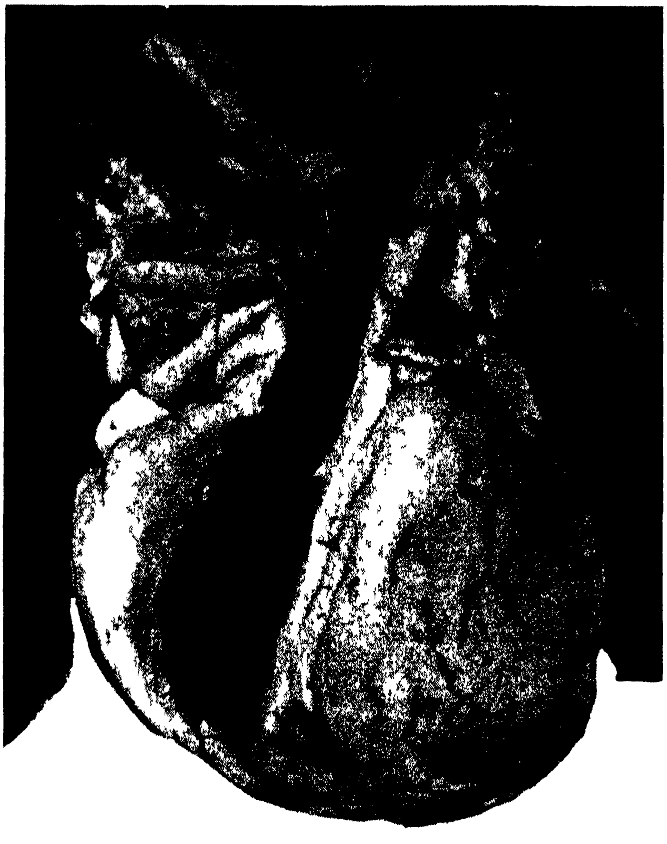

FIG 81 Pulmonary embolism. Note the coiled clot in the right ventricle.

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[1] " The Function of the Vertebral Veins and their Rôle in the Spread of Metastases," by Oscar V. Batson, Philadelphia, Pa., U.S.A., *Annals of Surgery*, 1940, **112**, 138. The method of investigation employed by Professor Batson was the injection of the deep dorsal vein of the penis, which communicates with the prostatic venous plexus, which in turn anastomoses with the lateral pelvic, sacral and vertebral veins, and these again having cranial and body-wall connections.

Effects of Embolism. The more immediate results of the obstruction are the same whether the emboli be "bland" or septic; but in the latter form there is, in addition to the degenerative changes, the softening action of the bacteria and their products. In the instance of the "bland" or non-septic embolus which produces complete obstruction of an artery, the general effects are the same as those brought about by thrombosis or by compression of the vessel; and, in discussing the subject, our statements are based on the results of ligature of the artery, and on artificial obstruction produced by means of tobacco- or other minute seeds, as well as the results of embolism as seen in disease. When an artery is obstructed, circulatory changes are first observed, but these are soon followed by nutritive disturbances and, later, both processes go on side by side. It is convenient, however, to describe the two stages separately.

Circulatory phenomena following complete obstruction of an important artery, *e.g.*, the superficial femoral:—

At first, the limb becomes cold, numb, and blanched, and pulsation in the artery beyond the obstruction ceases. If special care is taken to avoid damage to the limb, and if the vessels and heart are healthy, the limb, after a few hours, again becomes warm and red—even warmer and redder than the opposite limb. It may also become slightly swollen, and pulsation returns in the peripheral vessels. After a time, the circulation in the limb appears to have resumed its normal condition. The explanation of these changes is that anastomosing channels are gradually opened up, and a sufficiently complete collateral circulation is established. Degenerative changes in the vessels or in the heart and a low nutritive condition of the tissues may interfere with the production of a complete collateral circulation, and local death of tissue may occur in such cases before an adequate collateral supply is established. There are certain terminal or **end-arteries** in which the anastomosis with adjacent vessels is very limited and not sufficient to compensate for the obstruction. The most important end-arteries are:

(i.) The renal artery and its branches, especially the interlobular cortical branches.
(ii.) The splenic artery and its branches.
(iii.) The larger branches of the coronary arteries of the heart.
(iv.) The branches of the pulmonary arteries, especially those distributed to the surface and free margins of the lobes.
(v.) The arteries supplying the basal ganglia of the brain, and those supplying the grey matter of the spinal cord. The collateral supply of the cortical arteries of the brain and the spinal cord is less restricted, but is, nevertheless, only very limited.
(vi.) The central artery of the retina.
(vii.) The superior mesenteric artery, and some of the coronary branches to the stomach.

Obstruction of a branch of any of these vessels may lead to certain important changes in the area of supply.

INFARCTION

As has just been stated, obstruction of an end-artery leads to changes in the area of tissue supplied by that artery. Such an area becomes swollen, and often engorged with blood, and, on microscopical examination, every part of the tissue may be "stuffed" with red blood-corpuscles, hence the term "**infarction**" (*L. infarcio,* I stuff or cram) applied to it by Virchow. He named the affected area a "red" or "hæmorrhagic infarct." Infarction is produced by ischæmia. The area supplied by an end-artery which has been obstructed, lacks oxygen and undergoes necrosis. Such an area is not bloodless, for its veins and capillaries will contain the blood which was present at the moment of obstruction, but the flow of blood and the exchange of metabolites have ceased. As the degenerative changes develop in the area involved, the walls of the capillaries become more permeable, thus increasing the liability to the occurrence of hæmorrhage, The degree to which such hæmorrhage can occur is determined partly by the extent of the anastomosis with the vessels in the neighbouring living tissues and partly by the level of blood-pressure in such areas. Since capillary anastomosis, at least, is always present, it follows that every infarct has a hæmorrhagic border which develops in the zone where dead and living tissues are in contact. If the infarct is small, if it occurs when blood-pressure is high, and particularly if it occurs in an organ with rich anastomoses, this hæmorrhagic border may be, and usually is, sufficiently broad to fill in the entire area, and a **red infarct** results.

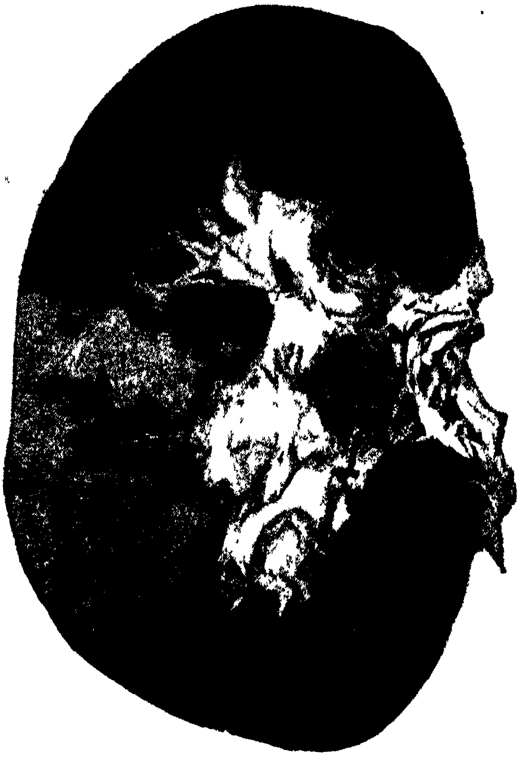

FIG. 82. *Infarcts in the Kidney,* showing wedge-shaped area, with a pale centre and darker (congested) periphery.

Obstruction of Branches of the Renal Artery. Areas of congestion of a purplish colour (infarcts) appear on the surface of the kidney a very short time after obstruction. These infarcts vary in size, number, and position according to the size, number, and distribution of the branches obstructed. They are raised above the surface, and, since the principal circulation of the organ has a radial pattern, are wedge-shaped, the base of the wedge being at the surface. At a later period, the **larger** infarcts show a **central pale area** surrounded by a broad red marginal band, the hæmorrhagic zone referred to above; but the **smaller** infarcts are **pale throughout,** and depressed below the surface. In cases of puerperal eclampsia, distinct necrotic areas are sometimes present in the kidney and, in certain cases, there is widespread thrombosis in the arterial branches and capillaries, producing very numerous infarcts, especially in the cortex, sometimes described as "cortical necrosis" (Fig. 499, p. 861). The thrombosis is probably the result of toxic action on the endothelium of the vessels.

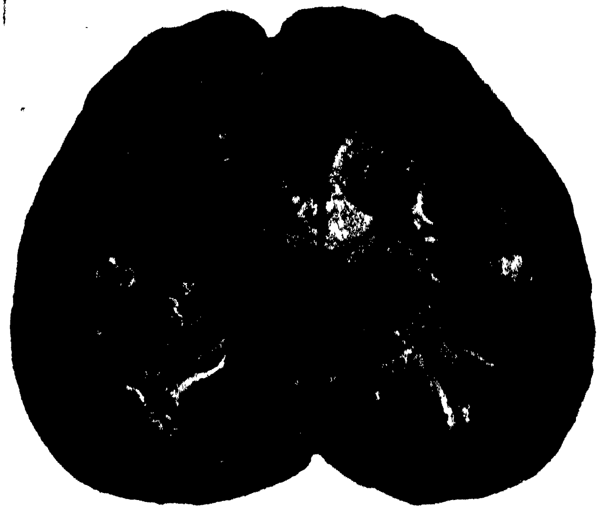

FIG. 83.—*Infarcts in the Kidney*, showing raised wedge-shaped area, with pale centre and congested hæmorrhagic periphery.

In our experience even the smallest infarcts are reddish and raised at first, but they very soon become pale; and, unless examined *in situ* within four or five hours after obstruction, this red colour has disappeared, and they are described as "pale infarcts." These red infarcts should not be described as "hæmorrhagic", as the colour is due to a temporary filling of the capillaries which passes off in a few hours. There is no actual hæmorrhage into the tissues of the kidney. When necrosis has extended throughout the infarct, the periphery often becomes infiltrated with leucocytes, and later it is invaded to a certain extent by connective-tissue cells and young blood-vessels. In this way the infarct, if small, may become completely absorbed; or, if of larger size, a definite capsule of fibrous tissue may be formed round it, and the central necrotic and usually amorphous part may undergo calcification. Very commonly, in a renal infarct, two areas in which the necrotic changes are not so advanced are seen—one immediately under the capsule, and the other forming, as it were, a bridge between the cortical and medullary part of the infarct, in the region of the boundary zone. These are parts where the collateral supply maintains the nutrition to a

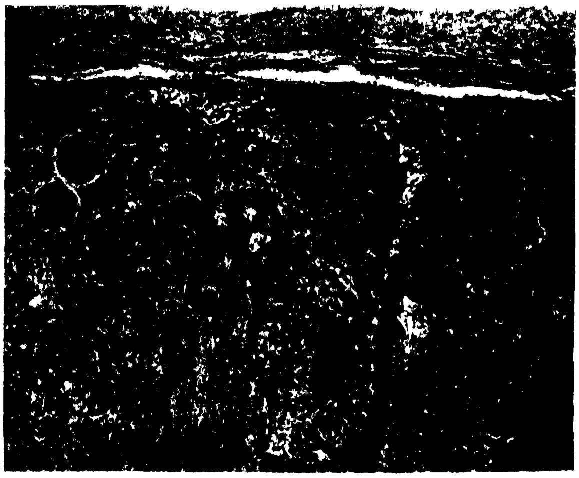

FIG. 84. Margin of an infarct in the kidney, showing pale area of necrosis on the left: and part of the surrounding dark zone of congestion and hæmorrhage on the right. Hæmatoxylin and eosin. × 40.

sufficient extent to prevent necrosis.

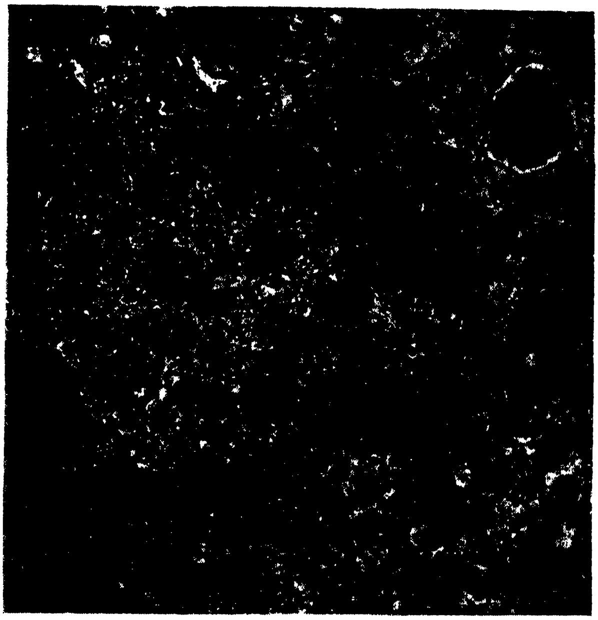

FIG. 85. The margin of an infarct in the kidney, showing, on the left, the more faintly-stained necrotic cortical tissues: and, on the right, congestion and hæmorrhage affecting the glomeruli and tubules at the periphery of the infarct. Hæmatoxylin and eosin. × 75.

Obstruction of Branches of the Splenic Artery. Splenic infarcts (*cf.* p. 692) are also irregularly pyramidal, with the base directed toward the capsule, but not quite reaching the capsule unless the infarct is large (Figs. 86 and 87). Elsewhere than at the poles of the organ, large infarcts usually show a transverse position with the longer axis of the base of the infarct at right angles to the long axis of the spleen. Small splenic infarcts are frequently hæmorrhagic, the larger ones frequently not. Necrosis takes place, and necrotic Malpighian bodies may be made out in the pale area. The pale area is usually surrounded by a narrow congested band, and in this band new fibrous formation takes place. As in infarction in the kidney, the degenerated area becomes cut off from the surrounding tissues by a definite fibrous capsule, and absorption of the degenerated area may occur with varying degrees of completeness.

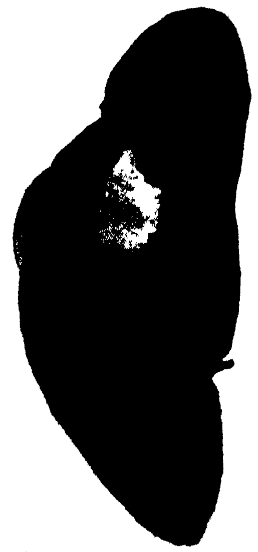

FIG. 86. Infarct in spleen, showing raised surface, transverse arrangement, and pallor.

Obstruction of the Coronary Arteries. Infarction of the Heart-wall is generally the result of thrombosis in diseased coronary arteries (*see* p. 467). Though obstruction of the right coronary artery may occasionally lead to myocardial infarction in the area of distribution of that vessel, and particularly of the upper portions of the posterior wall of the left ventricle and of the adjacent interventricular septum, the vessel most commonly affected is the descending branch of the left coronary artery, and, consequently, the commonest sites of infarction in the heart are (i) the anterior wall of the left ventricle near the apex; (ii) the anterior part of the ventricular septum towards the apex of the heart; and (iii) the posterior part towards the apex or other portion of the ventricular septum.

If death does not occur immediately, the part supplied by the thrombosed vessel undergoes necrotic changes. These necrotic areas or infarcts are generally irregular in shape and the central part is yellowish or dull white in colour and soft in consistence (**myomalacia cordis**). They are surrounded by a dark reddish zone of hyperæmia ; and frequently a peripheral infiltration with leucocytes, mainly of polymorphonuclear type, is observed. They may be hæmorrhagic. If the infarct extends inwards to the endocardium, thrombosis over the damaged area of endothelium takes place; and, at a later period, **aneurysm** and local fibrosis of the heart-wall may be produced (Fig. 268, p. 468). On microscopical examination, the necrotic muscle-fibres are seen to be in process of absorption, their place being taken by fibrous tissue (Figs. 269 and 270, p. 470). The layers of muscle immediately under the endocardium may not be affected. If they are necrosed, thrombosis will occur in the aneurysmal dilatation (Fig. 266, p. 468). If the area of necrosis is small, complete absorption of the necrotic muscle-fibres and their replacement by fibrous tissue may be the ultimate result.

FIG. 87. Old infarct in the spleen, showing pale necrotic mass surrounded by a fibrous-tissue capsule. Note depression below the general surface of the spleen. × 5.

Obstruction of the Pulmonary Artery (p. 521). **Infarcts of the lungs** are commonly multiple. They are wedge-shaped, with the base of the wedge at the surface, dark-red in colour, raised above the surface, and very firm. They are usually situated near the surface, and especially at the margins of the lung, though they may sometimes be found deeper in the lung-substance. They are commoner in the lower than in the upper lobe (Figs. 88 and 89). Over the base of all but the smallest infarcts a fibrinous pleurisy is usually present. On microscopical examination, the air-alveoli are seen to be filled with red corpuscles, and the alveolar capillaries are much distended with blood, and in consequence the sputum contains blood. Necrosis is usually present, but less extensive than in infarcts of other organs, probably owing to the very complete collateral circulation through the bronchial arteries, and therefore the comparatively slight impairment of nutrition. The decolorisation, which frequently occurs, is due merely to alterations in the hæmoglobin. Newly-formed fibrous tissue which is sometimes a sequel of the infarction may contain pigment derived from the broken-down red corpuscles.

Causes of Pulmonary Infarction. The condition of pulmonary infarction in the human subject is commonly associated with venous engorgement in the lung, due very often to mitral disease. In this condition of venous engorgement, thrombosis in, and hæmorrhage from, the distended vessels might readily occur ; and the infarctions are regarded by some authors as being due to this thrombosis and hæmorrhage. In some cases this is probably the actual explanation of the condition, but embolism from thrombosed systemic veins, *e.g.*, pelvic and prostatic veins, thrombosed and varicose veins in the legs, etc., must be given an important place as a causal factor. Large, pale, twisted or coiled emboli, originating as thrombi in the femoral, pelvic or other veins, become dislodged, pass to the heart, and are found partly in the right ventricle and partly in the pulmonary artery (Fig. 81, p. 171) or, in some instances, wholly in the latter. This condition of pulmonary embolism may complicate child-birth (p. 521) : or may follow operations, especially on the female pelvis, the prostate and the appendix. It commonly occurs from ten to fourteen days after the operation, though in some cases at an earlier period. These emboli, if large, usually cause sudden death before an infarct has had time to form ; or, if small, their occurrence may be indicated by hæmorrhage from the lung without other obvious physical signs. In cases of mitral disease with dilatation of the right side of the heart, thrombosis frequently occurs in the dilated right auricular appendix (auricle). Portions of this thrombus readily become detached, and are carried into branches of the pulmonary artery, but do not necessarily give rise to infarction. In those cases in which infarction is produced, general pulmonary congestion is always present, and is frequently associated with mitral stenosis, capillary

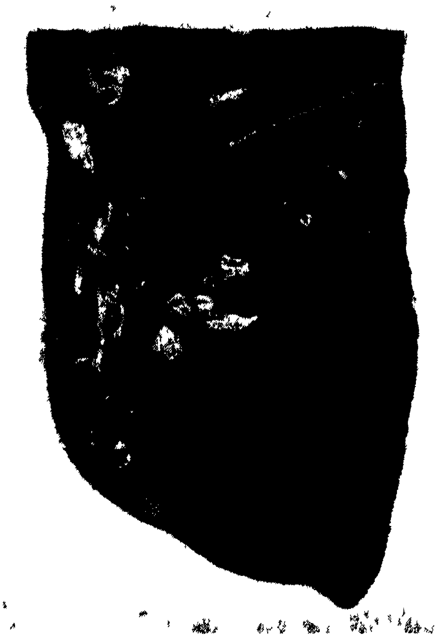

FIG. 88. Large pulmonary infarct, showing wedge-shaped, hæmorrhagic area towards lower margin of lung. The blocked branch of the pulmonary artery is seen in the upper left part of the dark infarcted area.

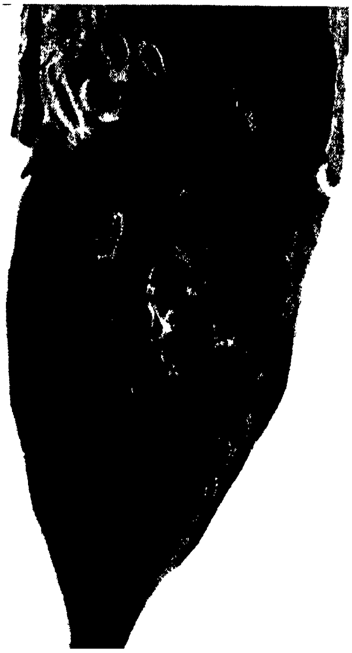

FIG. 89. Lung, showing dark irregular areas (infarcts), especially in the lower lobe.

engorgement, and high blood-pressure in the pulmonary veins. As a result of this engorgement, the collateral anastomosis with the bronchial arteries is not capable of maintaining a sufficient circulation in the affected area. Such conditions favour hæmorrhage. Hæmorrhages from the bronchi or into the air-cavities do not give rise to infarction. There is abundant evidence that during respiratory movements such blood becomes scattered and produces areas of collapse, which are surrounded by areas of distension of the air-cavities, conditions which are not seen in pulmonary infarction.

Obstruction of Arteries of the Brain (pp. 1028–34). The result of obstruction of the cerebral arteries, whether by embolism or thrombosis, is the softening of a portion of the area supplied. Hyperæmia is, as a rule, not a marked feature. The softening does not usually involve the whole area supplied by the obstructed artery, unless there is, in addition, widespread general arterial degeneration—a condition in which a collateral supply is not readily available. The infarct often becomes liquefied, and in great part absorbed, leaving, it may be, only a cavity or pseudocyst containing some milky fluid (p. 1034). **Obstruction of Arteries of the Spinal Cord** will lead to softening or **myelomalacia,** localised or widespread, according to the size of the vessel or vessels affected (p. 1167). **Obstruction of the central artery of the retina** results in sudden blindness with necrosis of the retina.[1]

Obstruction of the Mesenteric Artery produces hæmorrhagic **infarction of the intestine** with the rapid supervention of necrosis and gangrene (pp. 739–41). The superior mesenteric artery is the vessel usually involved.

Infarction in the **liver** is described on p. 765.

ŒDEMA OR DROPSY

In certain cases of venous obstruction, accumulations of clear watery fluid are found in the tissue-spaces or body-cavities, and to this condition various names have been applied. If the accumulation is in the tissue lymph-spaces, it is called **œdema** or **dropsy**[2]; whereas, if there is a general infiltration of all the subcutaneous and muscular connective-tissues, the name **anasarca**[2] is used. Accumulation in the peritoneal cavity is called **ascites**[2]; in the pleural cavity, **hydrothorax,** and in the pericardial sac, **hydropericardium.**

Part of the process of nutrition of the various tissues of the body is carried on by lymph, which in a normal individual transudes from the capillaries. This transuded lymph, altered, it may be, in composition, is reabsorbed by the lymphatics and the veins, and is thus carried back into the blood-stream. It has been shown by experiment that, if the pressure in the capillaries is increased, transudation takes place to a greater degree. The veins and the lymphatics may still be efficient channels for the absorption of this increased transudate, and no pathological accumulation of fluid then arises. If, however, there is considerable venous obstruction, there is interference with one of the paths of absorption, and the obstruction causes a further increase of pressure in the capillaries, and consequently a further increased transudation of lymph. If mere physical pressure were the only cause of abnormal increase of lymph in the tissues, there should always be found, in cases of increased transudation with diminished absorption, an accumulation of fluid in those tissues in the drainage-area of the obstructed vein. In certain cases of venous obstruction this dropsy does occur, but in other instances it is entirely absent. Where the femoral vein is obstructed, there may be considerable œdema of the tissues of the corresponding lower limb ; and, on the other hand, in some cases, on post-mortem examination, complete obstruction of even the inferior vena cava may be found without a trace of dropsy. It is thus clear that mere increase of pressure in the capillaries and diminished absorption by the veins are not in themselves the sole causes of the dropsy which so often follows obstruction of veins. It has also been shown by experiment that even extensive obstruction of lymphatic channels need not give rise to œdema. Other causal factors must therefore be considered, and we propose to study the condition in its most frequently occurring forms.

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[1] "Two Cases of Visible Emboli in Retinal Arteries: with a Histological Study (in one case) by W. E. Carnegie Dickson and Arnold Sorsby," by G. C. Pritchard and L. H. Savin. *British Journal of Ophthalmology*, Vol. **27**, 1943 (publication pending).

[2] These terms are confusing. **Dropsy** is a contraction of the old-fashioned word "hydropsy," and means simply an accumulation of "water" in the body, from the Greek *ὕδρωψ, hydrōps,* which is sometimes loosely and erroneously translated "a watery *appearance.*" **Œdema** is from the Greek *οἴδημα, oidēma,* from the verb *οἰδέω. oidĕō,* to swell or become swollen, and may be defined as swelling due to effusion of fluid into cellular tissue and particularly the subcutaneous cellular tissues. **Ascites**—Greek *ἀσκίτης νόσος. askitēs nosos,* the "baggy disease," from *ἀσκός, askos,* a skin made into a bag, and also applied especially to the belly, and hence comes to mean dropsy of the belly or peritoneal sac. **Anasarca**—Greek *ἀνά, ănă,* throughout, and *σάρξ, sarx, σαρκός, sarkos,* the flesh of the body, has come to be applied to an effusion into all the subcutaneous and muscular tissues.

Local Œdema. This may arise from obstruction to the blood-flow in a vein, *e.g.*, in the production of so-called " white leg " which sometimes follows thrombosis of the femoral vein. Similarly, ascites may result from portal obstruction in cases of cirrhosis of the liver. Interference with lymphatic drainage by cancerous growth may produce local œdema of the drainage-area ; thus in cancer of the breast there may be œdema of the arm. Not uncommonly, however, both veins and lymphatics are obstructed in such cases. The thoracic duct may be blocked by malignant growth, tuberculous lymph-nodes or parasites (*e.g.*, *Wuchereria* or *Filaria bancrofti*) ; and a common result is rupture of some of the lacteals in the mesentery and the production of chylous ascites. Elephantiasis of the leg or scrotum is a local œdema accompanied by inflammatory and fibrous changes following the multiple blockage of lymphatics by the filarial ova and embryos (*see* pp. 424–6). (*See also under* " Angio-neurotic Œdema," p. 181.)

Cardiac Œdema. This occurs in cases of venous engorgement where there is central obstruction to the circulation from valvular disease of the heart, or from general cardiac weakness. The œdema shows itself first in the feet and legs, if the patient is in the upright position, or in the tissues of the back or in the dependent parts of the lungs, if he is lying down. This suggests that gravity and general venous congestion are amongst the more important factors concerned. But, in such cases, the long-continued increase in the venous and capillary pressure produces changes in the endothelial lining and in the other structures of the walls of the veins, so that to a considerable extent they lose their contractile power, and the diminished oxygen-content of the blood means diminished nourishment to the lining-cells, with consequent degenerative changes and increased permeability. On the much debated question of the selective secretory or excretory capacity of the vascular endothelium in this connection, it need only be said that, if the lining-cells perform such functions, these must become deranged as a result of pathological changes in the endothelium itself. In addition, the tissues round the dilated vessels, partly from pressure of the distending fluid and partly from malnutrition, undergo a certain amount of atrophy and degeneration. Their elasticity, and consequent onward driving power, are much diminished. The perivascular lymphatics, and probably also the small venules and capillaries, are not functioning efficiently, and the vasomotor nervous control may also, to a certain degree, be lost. Further, the accumulation of waste-products in the blood or in the surrounding tissues may disturb the normal process of osmosis and so attract more water from the blood. All these factors will favour the accumulation of lymph in the tissues, but it is difficult accurately to estimate the relative part played by each. From experimental evidence, the main factors seem to be the increased permeability of the walls of the dilated capillaries and increased hydrostatic pressure within them. We believe that the increased permeability of the capillary-wall is the main factor, and that increased vascular pressure, though important, is quite secondary as a causal agent. This increased permeability may be due partly to actual damage to the endothelial cells by bacterial toxins and other poisons, and partly to a disturbance of the normal process of osmosis by the presence of these poisons in the blood or in the surrounding tissues. For the influence of vitamins, including *vitamin P*, upon vascular permeability, see below, and also pp. 137 and 443.

Nutritional Œdema. Under this term are included, not only the œdema which occurs during times of war and famine (famine œdema), but also the œdema found in wasting diseases such as tuberculosis, cancer, and diabetes, and in anæmia (cachectic œdema). In all such cases, there is a deficiency in the plasma-protein content of the blood, but there is also associated cardiac weakness and a hydræmic condition of the blood itself. If the amount of fluid which transudes into the tissues through the walls of undamaged capillaries is the result of the capillary blood-pressure and the osmotic pressure of the plasma-protein, it follows that this balance may be disturbed by alterations in the capillary blood-pressure or in the content of plasma-protein. In famine, the low protein-intake leads to a lowered plasma-protein concentration and therefore to a greater transudation of fluid into the tissues and a lessened absorption, with consequent œdema. This protein-deprivation occurs also in cachexia. But the cardiac weakness, the hydræmic condition of the blood, and the presence of toxic or metabolic substances in the blood and in the tissues must play some part in the production of this condition, by causing nutritive changes in the tissues themselves and especially in the vascular endothelium, leading to an increased permeability. It is generally accepted that the œdema and effusions of beri-beri are due to protein-deficiency rather than to avitaminosis *per se* (in which connection *see also* pp. 443–4).

By giving to rats a diet deficient in protein, œdema is produced when the protein-concentration has fallen below 4 per cent.; and in dogs the lowering of the plasma-proteins to 3 per cent. brings about subcutaneous œdema and general anasarca.

Renal Œdema (p. 881). Of this there are two main types, one which occurs early in acute glomerulo-nephritis in which clinically the œdema is noticed especially in the loose cellular tissues, for example, about the eyelids : and the other in the subacute or chronic renal disorder known as nephrosis, in which the glomerular changes are slight, but the œdema is widespread in the skin and subcutaneous tissues. In the former there is no appreciable fall in the plasma-proteins ; and the blood-flow through the kidney is greatly reduced, with consequent diminution or even arrest of the secretion of urine. The blood-volume may be increased and there is a rise in blood-pressure. The production of the œdema seems to be due mainly to the increased blood-pressure and the increased capillary permeability to proteins—possibly brought about to some extent by toxins. In the latter condition—nephrosis—there is extensive œdema, with serous effusions, a great loss of protein, almost wholly albumin, by the urine, and considerable disorder of lipoid metabolism. The œdematous fluid has a comparatively negligible protein-content (about 0·1 per cent. compared with 0·5 to 1·0 per cent. in acute glomerulo-nephritis). It seems clear, therefore, that capillary permeability to proteins is not increased. On the other hand, the abundant albuminous content of the urine and the almost entire absence of globulin suggest that the glomerular permeability to the smaller albumin-molecules has been profoundly altered. The plasma-protein osmotic pressure is greatly reduced (Samson Wright states that 1 gramme of albumin exerts an osmotic pressure of 6 mm. of Hg., while 1 gramme of globulin exerts an osmotic pressure of only 1·5 mm. of Hg.). The normal osmotic balance between the blood and the tissues is thus seriously deranged and an excessive amount of fluid transudes into the tissue-spaces and remains there. This lowering of the plasma-protein osmotic pressure seems to be the chief factor producing the œdema. It is unnecessary to deal with the former view that salt-retention was the cause of renal œdema. This hypothesis cannot be maintained for several reasons, *e.g.*, the kidneys may still have the power of excreting chlorides when œdema is present, and the œdema is not invariably related to this retention.

Angio-Neurotic Œdema. Our knowledge of the actual causes of the types of œdema occurring in vasomotor and other " nervous " disorders is still very imperfect. The forms associated with acute and transitory œdematous swellings in the throat (p. 504), joints and subcutaneous tissues (pp. 135–6), and with urticarial, vesicular and other trophic disturbances of the skin (pp. 136–7), are **allergic** in nature. These phenomena may be associated with certain nervous disorders : or with the presence of some variety of circulating foreign protein (pp. 136–7) : or they may be the result of defective or aberrant nutritional factors (p. 180). Certain less transitory and more chronic types of œdema are seen in patients suffering from hemiplegia and other lesions of the neuraxis, and are no doubt at all events in part due to the effects of the nervous disorder upon the blood-vessels and lymphatics ; but the loss of tone of skeletal muscle, as well as of the muscular coats of the vessels themselves, must also conduce to the production of dilatation of the vascular channels and the loss of propulsive power.

Inflammatory Œdema. This is described in the chapter on Inflammation (pp. 17–18). In this type of œdema, though there is undoubtedly increased pressure in the capillaries, the most important factor seems to be an alteration in their vascular endothelium. The vessels become much more permeable, and proliferative and degenerative changes can be demonstrated in their lining-endothelium. This fluid is usually described as an " exudate " in contrast to those occurring in the other types which are designated " transudates."

Conclusions. From what has been said above, it will be seen that, in the causation of œdema or dropsy, the following factors must be considered :—

1. Alteration in the vascular walls, produced by malnutrition (including any vitamin-deficiency), disease, prolonged dilatation, and toxic or metabolic poisons in general—these causes leading to an increased permeability.

2. Increased pressure in the capillaries, due to obstruction to the circulation in the veins by thrombosis or by pressure of tumours, etc.

3. Pathological conditions in the heart, due to valvular disease or general weakness. These may act by causing increased pressure on account of the venous stasis.

4. Alterations in the blood itself, such as oxygen-deficiency, increase in the watery element, a relative diminution in the proteins, and the introduction of waste-products or toxins.

5. Starvation of the tissues, and the accumulation in them of metabolic products which alter the osmotic pressure or demand from the vessels, in some unknown way, an increased flow of lymph.

W. E. Le Gros Clark [1] states that "it has been recently demonstrated that fibroblasts probably play an important *rôle* in the process of water-retention in the tissues; hence they have a considerable significance in regard to problems of pathological œdema or dropsy." O. E. Aykroyd and S. Zuckerman[2] have noted that, in the skin of the genital region of *Rhesus* monkeys, under the influence of œstrogenic stimulation, the cells show wide fluctuations in size under different conditions of tissue-hydration, and they believe that this indicates that the cells have the property of taking up water from the surrounding medium, and so leading to a local concentration of the tissue-fluid. The connective-tissue cells appear, therefore, according to these observers, to be essential factors controlling the regional distribution of body-fluids in the connective tissues of the body; and glial cells may perhaps exercise a similar function in the central nervous system (pp. 1027–28).

Composition of Œdema-Fluid. The fluid corresponds approximately to ordinary lymph, but often has a smaller proportion of proteins. Thus, in inflammatory œdema the protein-content is practically the same as that of normal lymph; whereas in the œdema of chronic renal disease it may fall to 0·1 per cent. or even lower. The specific gravity is usually low, 1·006 to 1·012, but in inflammatory œdema it may be 1·015. The fluid of inflammatory œdema may contain polymorphonuclear and other inflammatory cells; but that from cardiac or renal cases shows very few cells, and these mainly mononuclear in type. Sugar, bile, uric acid, etc., may be present in varying amounts in different cases.

MECHANICAL AND PHYSICAL INJURIES—SHOCK

Severe mechanical injuries of a crushing or lacerating nature, and especially those in which the abdominal viscera are exposed and crushed, are liable to be followed by severe shock. Shock may also be associated with perforation of the wall of the stomach or intestine, strangulated hernia, a severe blow on the abdomen without obvious physical injury, a blow on the testicle, severe physical pain, extensive surgical operations, abdominal, thoracic or cranial, especially if the anæsthesia is not sufficiently deep, intense septic infection, extensive burns especially of a superficial nature, severe hæmorrhage (p. 663), and painful mental impressions. Exposure to cold and lack of food and water, aid in the production of shock.

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[1] "The Tissues of the Body." Oxford, Clarendon Press, 1939, p. 36.

[2] "Factors in Sexual-skin Œdema." *Jour. Phys.*, 1938, **94**, 13.

There is disturbance of the various functions of the body, with associated depression, dulling of sensitivity and lowering of blood-pressure. The skin and mucous membranes are pale, and beads of cold sweat are seen on the skin, the eyes are sunken, and restlessness with dull torpor but not unconsciousness is present. The pulse is rapid, irregular and feeble, the temperature subnormal and respiration weak, irregular and shallow. The symptoms may appear immediately after the occurrence of the injury—primary shock—or they may be delayed for a few hours—secondary or delayed shock.

The primary form is due probably to a sudden reflex nervous reaction producing an inhibitory action on the heart itself through the vagus nerve. There is dilatation of the vessels in the splanchnic area, a diminished return of blood to the heart and, therefore, an imperfect filling of its chambers during diastole. In delayed shock, a considerable drop in blood-pressure, followed sometimes by a temporary rise due to contraction of the arterioles, takes place. As a result of this low blood-pressure, the pulse may be so feeble that it cannot be felt at the wrist. There is a great diminution in total blood-volume and the heart receives a much diminished amount of blood. The suggested explanation of these changes is that, as a result of a loss of tone in the capillaries, dilatation takes place and the walls become more permeable. This permeability increases the filtration of fluid into the tissues and the blood thus becomes more concentrated. It is said that the blood in the capillaries may contain two million more red corpuscles per cubic millimetre than that in the venules. In patients suffering from wounds or bruises, there may be hæmorrhage into the tissues, which will further lessen the blood-volume. The diminution of the blood-supply to the heart and to the brain interferes with the vital centres and death may follow from failure of the respiratory centre. It has been suggested that, with the shock following injuries, especially burns, or accidents resulting in crushing and laceration of muscle, some depressor-substance, allied to histamine, is liberated and acts as a generalised poison (p. 145). It is at all events true that injections of histamine produce symptoms similar to those occurring in shock after injuries. By its direct action, a dilatation of the capillaries at the site of injection and an increased permeability of their walls with resulting œdema takes place. In addition, through the medium of a reflex mechanism, there is also a widespread dilatation of neighbouring arterioles. If histamine finds its way into the general circulation, a subsequent dilatation of the small vessels takes place with a resulting depletion of the main vessels of the heart, which depletion is exaggerated by the increased permeability of the walls of the vessels. The blood-pressure is lowered, the blood-volume is reduced and the blood becomes more concentrated as a result of the filtration of fluid and plasma-proteins through the walls of these dilated capillaries. Histamine itself in varying amounts can, according to Abel, be extracted from every individual tissue, and he considers that this substance is the active agent producing the vascular changes associated with shock. Other workers consider that histamine or some choline-derivative plays some part, but is not the only agent concerned in the process. Histamine is present in only very small amount in muscle and no " depressor " substance has been isolated from the blood in cases of shock, and therefore a definite case for this toxæmic cause has not been made out. At present there is no general agreement as to the cause of shock, but it can be stated that, in all cases, diminution in blood-volume and dilatation and increased permeability of the capillaries are the most important ascertainable phenomena, and that such conditions must lead to impaired action of the heart and impaired blood-supply to vital centres in the brain.

INJURIES DUE TO HEAT

Burns and Scalds. Damage to the tissues by dry heat, or by the electric current (including lightning) constitutes a **burn,** and the lesions produced by strong acids and caustics are similar in character. In a **scald** the lesion is caused by hot liquids or vapours. Radium and X-ray " burns " are really areas of necrosis, due to the actinic and photo-chemical destructive action of the rays upon the sensitive cells of the tissues, more particularly if these are undergoing mitotic division.

The danger to life depends, not merely on the depth to which the tissue-damage has penetrated, but also on the extent of the body-surface involved and, perhaps to a less extent, on the actual site of the burn. There are no distinctive post-mortem appearances, apart from the actual local destruction of tissue at the site of injury, in cases of death after severe burns. There may be congestion of the brain and meninges, and of the mucosa of the digestive tract, occasionally with small hæmorrhages in the latter. The duodenal ulcers, which have been described, are very rare. The red corpuscles undergo disintegration, and there is frequently an excretion of hæmoglobin by the kidneys. Death, when it occurs, is usually due to shock. This may be primary or secondary. In the secondary type, the diminution in blood-volume is due probably to the considerable exudation from the thrombosed, damaged and dilated capillaries and other vessels of the injured area. The more extensive the burn, the greater is the exudate and the lower the blood-volume. Death may take place during this stage, but, in untreated or imperfectly treated cases, is more liable to occur in the toxæmic stage, *i.e.*, about the second or third day after the original injury. At this stage, the symptoms are those associated with absorption of toxic substances produced by tissue-autolysis and also, in many cases, by bacterial invasion and multiplication. The pathological lesions found after death may be those commonly seen in cases of septicæmia or pyæmia.

This is more apt to be true of those dying after the third day, but, with secondary pyogenic infection of burned areas, deaths from pyæmia may occur weeks after the injury had been received. Pneumonia is also a frequent cause of death occurring five days or more after burns. Burns have been divided into various **grades** or **degrees** of **severity**. Some authorities recognise six degrees and others only four. For descriptive purposes it is convenient to deal with the pathological lesions under six types.

1. Burns characterised by superficial congestion of the skin (**erythema**), without destruction of tissue.
2. Those in which a certain amount of œdema with the formation of **blisters (vesication)** is present. Permanent discoloration may follow this lesion.
3. Those in which destructive changes involve the **supporting vascular tissue of the cutis vera** or **dermis,** extending to the tips of the interpapillary processes which, with the sensitive nerve-terminals, are laid bare and left intact.

The sweat-glands, sebaceous glands and hair-follicles are not destroyed. Because of the survival of so many epithelial elements, there is rapid replacement of the epithelium over the newly-formed granulations. The resulting scar undergoes no contraction. Burns due to explosion of shells or bombs are often of this type.

4. Those characterised by destruction of the **whole thickness of the skin** with some damage to the **subcutaneous tissues.** In these, the base of the wound becomes a mass of granulation-tissue ; healing is slow and is usually associated with sepsis, with **eschar-formation,** frequently leading to the formation of **fibrotic contracture.**

5. Those in which **all the soft tissues** are involved, including muscles and fasciæ, vessels and nerves.

6. Those in which complete **carbonisation** takes place.

In prognosticating the outcome, the **proportion of the body-surface involved** is often of as much, or even of more, importance than the degree of burning. The treatment of **shock,** primary and secondary, by the recognised methods, including morphia and the intravenous transfusion of plasma or of " reconstituted concentrated serum " (*not* whole blood or saline) to counteract the " hæmo-concentration " or fluid-imbalance due to shift and loss of fluid from the circulating blood into the tissues (p. 183) is of great importance. These changes in the circulating blood can be estimated by noting the rise in hæmoglobin—perhaps to 120 or 140 per cent.—and the degree of corpuscular concentration. After any necessary preliminary cleansing, **immediate treatment** of the burn itself, *e.g.*, with powdered sulphanilamide : hypochlorite-solution : or an appropriate coagulant application such as tannic acid, silver-nitrate solution, or some suitable dye or admixture of dyes, for example gentian violet, brilliant green and euflavine or neutral acriflavine, either as a spray or in the form of a triple-dye jelly such as " triofax," or repeated spraying with sulphadiazine (" sulfadiazine "), renders the prognosis more favourable by causing a drying-up of the tissues and hindering or inhibiting bacterial growth.

If burns of the fourth, fifth and sixth degree undergo healing, a cicatrix is formed and this, by its contraction, produces deformity. Such a cicatrix may present itself as a dense fibrous mass, which is merely a hyperplasia of the scar tissue. This is the condition described as **cheloid,** which may occur also in the healing of other wounds and especially those of tuberculous patients and in negroes (pp. 54, 268–9 and 301). In the later stages of cicatricial contraction after " burns," whether due to the action of heat (or cold—for the effects of these are similar and analogous), X-rays, radium, or even excessive exposure to sun-light,[1] squamous-celled **carcinoma** may develop from the regenerated epithelium overlying the scar.

INJURIES DUE TO COLD

It is a common experience that the results of exposure to cold depend upon two main factors : the individual susceptibility, and the degree and duration of the exposure. An attack of rheumatism or pneumonia is frequently said to be due to " getting cold " or " wet," or sitting in a " draught " ; and, though it is known that both of these diseases are infective in their origin, yet it is true that exposure to cold or damp does render certain persons liable to an attack, and these are rightly considered as predisposing causes. The mechanism of this causal relationship is not clear ; but that some definite change is brought about by such exposure is undoubted. It has been said that the chilling of the skin produces contraction of the superficial, and congestion of the deeper, vessels and those in the internal organs, but, though this may play some part, it does not seem to be the whole explanation.

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[1] " Review of Irradiation Effects on Cells and Tissues of the Skin," by W. F. Harvey, R.C.P. Laboratory, Edinburgh, *Edin. Med. Jour.*, 1942, **49,** 529.

In some people, especially those with defective circulation and whose diet is deficient in vitamins such as vitamin D (p. 440), and particularly in children, **chilblains**, an inflammatory hyperæmia of the fingers, toes and ears may develop on exposure to cold. In severe cases, blisters may form and on bursting produce ulcers.

Exposure to severe degrees of cold, especially when associated with wind and moisture, produces, in some people, slight, and in others severe, injuries dependent largely upon the contraction of the vessels and the resulting ischæmia. Their fingers and toes become cold and cyanotic, and may swell and become inflamed, and small areas of necrosis may develop.

If the cold is still more severe and its application prolonged, more serious results, such as **frostbite,** are produced. The cell-destruction is more intense, and this, aided largely by the prolonged ischæmia from the extreme contraction of the blood-vessels or even from their thrombosis, produces gangrene of the extremities. The feet or the toes become livid or cyanotic, swollen and cold, and turn purple, or, eventually, greenish-black. The necrotic and gangrenous areas become sharply demarcated and dry up, or, if much moisture remains, undergo putrefactive changes (*see under* Gangrene, p. 251).

Trench-Foot or Trench-Frostbite: and Shelter-Foot. The essential changes in these conditions consist in damage to the blood-vessels and the consequent production of vasodilatation and inflammatory œdema or exudative inflammation. According to Lorrain Smith, J. Ritchie and James Dawson (1915),[1] the damage in trench-foot is shown by the swelling of the endothelial cells in the blood-vessels of all kinds, and by the vacuolation of the muscle-fibres in the arterial walls. In consequence of these degenerative changes, an excessive amount of fluid is poured into the tissues, and this brings about degeneration of the cells, separates the connective-tissue fibres from one another, and interferes with absorption by the lymphatics. All these factors may, in the severer cases, lead to the production of necrosis, and sometimes they are associated with emigration of leucocytes and other phagocytic cells, the functions of which are the removal of the products of tissue-destruction. No doubt the exposure to cold, in muddy water-logged trenches or trench-shelters, especially in winter, and the muscular inactivity, must be regarded as the primary cause of the damage to the vessels. At the same time, it seems clear that pressure and constriction by imperfectly-fitting boots, and, in the War of 1914–18, by puttees, and venous stagnation, played a considerable preliminary part in producing these degenerative, necrotic and gangrenous changes. Lesions analogous to those of trench-foot may occur after shipwreck and are known as **immersion-foot.**

In contrast with these well-recognised deleterious effects of the action of cold, it has been suggested that **temporary refrigeration** of crushed and even gangrenous limbs may be beneficial and perhaps life-saving as a preliminary to operation—giving the patient time to recover from shock and other ill-effects of trauma and allowing the surgeon to postpone immediate interference whilst the patient is less hurriedly prepared for operation : but useful more especially in affording the surgeon a " bloodless and shockless field of operation " (*see* note on p. 256).

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[1] " Clinical and Experimental Observations on the Pathology of Trench Frostbite," *Jour. Path. and Bact.,* 1915, **20**, 159.

"RAYNAUD'S DISEASE." The symptom-complex or syndrome often described under this name can be produced by a variety of pathological lesions. It affects especially the hands, though the feet, the ears and the nose may be involved. In the hands, the digital arteries undergo extreme contraction as the result of spasm of the muscular coat, first at the finger-tips, but gradually extending to the bases. There is numbness and loss of function and blanching of the skin due to the contraction of the venules and the emptying of the capillaries. Recovery usually takes place, but repeated attacks may give rise to small areas of necrosis. The condition commonly follows the action of cold with resulting vaso-constriction. Following the blanching and sometimes independent of it, the affected part becomes livid and swollen. This is due probably to the arteries remaining constricted, while the capillaries and veins become dilated. When necrosis or gangrene supervenes, the cyanosis is very intense and small blisters are sometimes present. There is no evidence of thrombus-formation in the arteries, and their spasmodic contraction is due apparently to a hyperexcitability of the vasomotor centres. Degenerative lesions are found in the corresponding sympathetic or autonomic ganglia (*see* Figs. 764 to 768, pp. 1193–97), and ganglionectomy of these in the lower cervical or lumbar region has been attended with favourable results. In connection with "Raynaud's disease" of the upper limbs, the ganglia most frequently removed are the inferior cervical and first thoracic, which in the course of development have often become coalesced and are then known as the "stellate" ganglion (Figs. 764 to 768, pp. 1193–97), and the best results are obtained if the operation is planned to interrupt the *pre*-ganglionic components of the peripheral vasoconstrictor pathway, as with the technique of Smithwick and Telford. Bilateral sympathectomy is also of value in cases of thrombo-angiitis obliterans (pp. 244 and 483) associated with Raynaud's syndrome.

ACTIVE HYPERÆMIA

Active hyperæmia of any part of the body is due to an increased afflux of blood to it. The part, if on the surface, can be seen to become of a reddish colour, the local temperature is raised, and there may be some swelling. The arteries and capillaries of the hyperæmic area are dilated, and the blood-flow is increased in rapidity. There may also be an increase in the normal lymph-transudation, though this is not as a rule pronounced, and is not an important factor in the process. The essential change in all cases is the arterial dilatation, and this may occur under a variety of circumstances.

I. **Physiological.** When special organs are called into functional activity, the arterial supply is increased. This is physiological, and is necessitated by, among other factors, the extra nourishment required, for example, by the uterus during pregnancy or the mammary glands during lactation.

II. **Pathological.** In studying pathological dilatation of arteries, it is often very difficult, or even impossible, to determine the ultimate cause. There are many factors to be considered, and these interact on one another in almost all cases. Alterations in the walls of the arteries may be caused by interference with the nerve-supply; or pathological conditions of the innervation may be due to degenerative conditions of the vascular walls. Again, interference with the blood-supply may cause both damage to the nutrition of the vascular walls and derangement of the nervous control. It is convenient to study each group of cases separately.

1. **Hyperæmia caused by the Direct Application of Mechanical, Chemical, Thermic, or other Analogous Forms of Irritant** (p. 15). Exposure of the frog's mesentery to the air, or to irrigation by a 1·5 per cent. salt-solution, is sufficient to set up active hyperæmia in it. Similarly, the application of alcohol, ether, ammonia, mustard or cantharides, to the skin or mucous membranes is followed by local arterial hyperæmia. Nitrites cause arterial dilatation by producing relaxation of the non-striped muscle of the arterial wall.

A tight ligature applied to a finger produces ischæmia of the part, and, on removal of the ligature, is followed by active hyperæmia ; and a similar reaction follows the temporary application of cold. In most of these cases, and certainly in those in which the nutrition of the vascular walls has been impaired by even a brief period of deficient circulation, the vascular dilatation is not wholly, or even predominantly, the result of stimulation of the vaso-dilator, or of paresis of the vaso-constrictor, fibres which pass to the blood-vessels in and from the sympathetic nerves[1] ; for, if these nerves are cut, the dilatation can still take place. The reaction is thought to be due, in part at all events, to the direct action of histamine or some allied substance (pp. 145 and 183–4), liberated from the tissues by the mechanical disturbance caused by the ligature. When present in the skin, this substance, whatever be its nature, leads not merely to the production of local dilatation of capillaries and venules but also dilatation of the neighbouring arterioles by a local reflex action associated with the sensory nerve-endings in the skin and the numerous collaterals which these give off to the arterioles in the neighbourhood. The hyperæmia thus produced, may be pronounced, and the distension so great that rupture of poorly supported capillaries or venules may take place. This is sometimes seen when a distended bladder is too quickly emptied by catheter. The ill-supported vessels in the mucous membrane, owing to the sudden relaxation of the pressure to which they have been subjected, become rapidly over-distended with blood and rupture, with the production of extensive hæmorrhage into the bladder.

2. **Hyperæmia due to Vaso-constrictor Paralysis and Vaso-dilator Stimulation.**[1] Section of the main sympathetic trunk in the neck in animals is followed by arterial dilatation and redness in the corresponding half of the head and neck. The same result is sometimes seen in the human subject, as a consequence of pressure upon the nerve by tumours, enlarged lymph-nodes, etc. Reflex vaso-motor influence leads to hyperæmia, *e.g.*, in blushing. References to the removal of the stellate ganglion for the treatment of Raynaud's syndrome will be found on pp. 167, 187, 483 and 1193–97. The stimulation of vaso-dilator fibres probably also plays some part in certain cases ; and the erythemas of the skin—seen in the area of distribution of an injured nerve—the erythemas in other conditions, the rashes in fevers, and the wheals in urticaria may be due, at all events in part, to this stimulation. In the infective conditions above noted, the toxins may act as vaso-dilators, but, undoubtedly, damage to the vascular walls by these toxins plays an important part in bringing about the active hyperæmia.

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[1] For details of the vaso-constrictor and vaso-dilator nervous mechanisms at work in the production of these various reactions, the reader should consult Samson Wright's *Applied Physiology*, 7th edition, Oxford University Press, 1940, pp. 446, 456, and 467–8 *et passim.*

CHAPTER VIII

GENERAL RETROGRESSIVE CHANGES

CELLS and tissues, whatever their structure or function, may be damaged by injurious agents in various ways. They may be acted upon *directly*, *e.g.*, by a corrosive acid on a skin or mucous surface, or *remotely*, as when a bacterial toxin is carried to them by blood or lymph. They may be affected *indirectly* through the nervous system or by disturbances in the endocrine system.

The term **Necrosis** is applied to the process in which death of cells or tissues occurs in the living body. When putrefactive processes also supervene, the term **Gangrene** is employed. **Atrophy** is a gradual loss of substance and a form of regressive change.

Other regressive changes are the various forms of **Degeneration** and **Infiltration,** which are often combined. A **Degeneration** may be defined as a condition characterised by the transformation of the cell-protoplasm or the tissue-structure into useless or abnormal substances. An **Infiltration** is the accumulation within the cell or tissue of useless or abnormal substances or of normal substances in abnormal amount. In both instances, the cell or tissue is damaged, and often the degree of damage determines the nature of the retrogressive process. Thus a cell severely injured may undergo disintegration of its component parts and be unable to utilise metabolic products brought to it; whilst a cell less seriously injured may still carry on its functions in part, but be unable to utilise all substances brought to it, which thus accumulate in, or infiltrate, it. Such substances as food-material, *e.g.*, glycogen or fats, or products of metabolism, *e.g.*, pigments, urates, etc., may thus accumulate. The process may be temporary or permanent.

From what has been indicated above, it will be understood that, the more highly-endowed an individual cell is with regard to its special function, the more easily may its delicate mechanism be thrown out of gear; and hence it is that certain highly complex, and at the same time extremely delicate, cells are more liable to injury than are the hardier and less highly-differentiated cells of the body. When so damaged, such highly-endowed cells have also, as a rule, much less power of recovery. Nervous, glandular, and other highly-specialised cells are much more liable to suffer from injury and disease than are, say, the less differentiated cells of a supporting connective tissue. Again, certain toxic agents have a special selective capacity for certain cells or tissues, and may cause their destruction, at the same time leaving other cells and tissues practically unharmed. Thus the toxins of the bacillus of tetanus act specially on certain nerve-structures, whilst those of the diphtheria bacillus act more particularly on some of the secretory cells of the kidney or on heart-muscle.

Interference with cell-respiration, as in anoxæmia (p. 157), is an important factor in causing cell-degeneration.

DEGENERATIONS AND INFILTRATIONS

CLOUDY SWELLING

The term "cloudy swelling" (*cf.* p. 13) covers a variety of changes, often referred to generally as "toxic." In its less severe form, the condition would appear to be reversible and a return to the normal possible; in its severer forms, further damage may result, and thus all gradations from cloudy swelling to actual disintegration of the cell may be seen. The changes depend partly on the nature of the causal agent and partly on its severity and the duration of its action. If a virulent toxin gains free access to a cell, such cell may be killed outright without time for the development of cloudy or fatty changes. In the early stages of autolysis, appearances similar to those of cloudy swelling are seen in cells (*see* pp. 234–5).

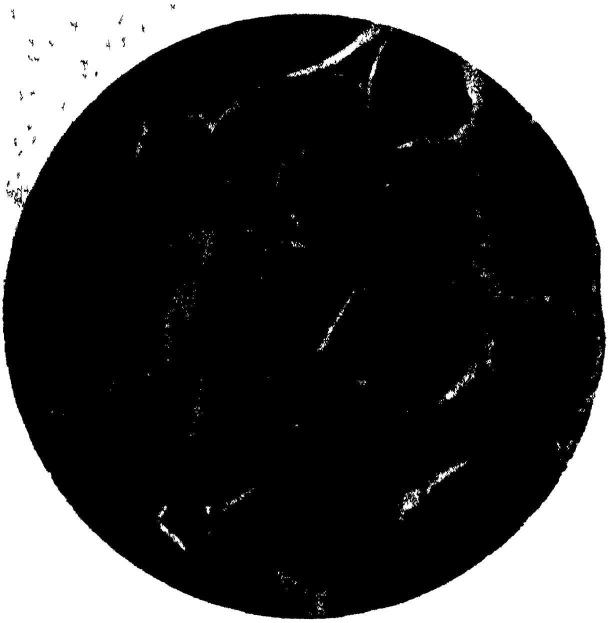

FIG. 90. Convoluted tubules of normal kidney to show the regular rods of mitochondria in the cells of the tubules. Hæmatoxylin and eosin. × 1000.

Cloudy swelling is known also as **turbid swelling, parenchymatous** or **albuminoid degeneration.** The swelling of the cell is due to imbibition of fluid, and the granular and vacuolated appearance to changes in the cell-structure. The granules, in the earlier stages, are soluble in weak acid or alkali, and take up eosin stain. Detailed examination has shown that they are due, in part at least, to changes in the mitochondria.[1] Thus, in the case of the cells of the convoluted tubules of the kidney, the normal mitochondrial

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[1] J. Lorrain Smith and Theodore Rettie, *Jour. Path. and Bact.*, 1925, **28**, 627, and R. F. Ogilvie, *ibid.*, 1932, **35**, 743.

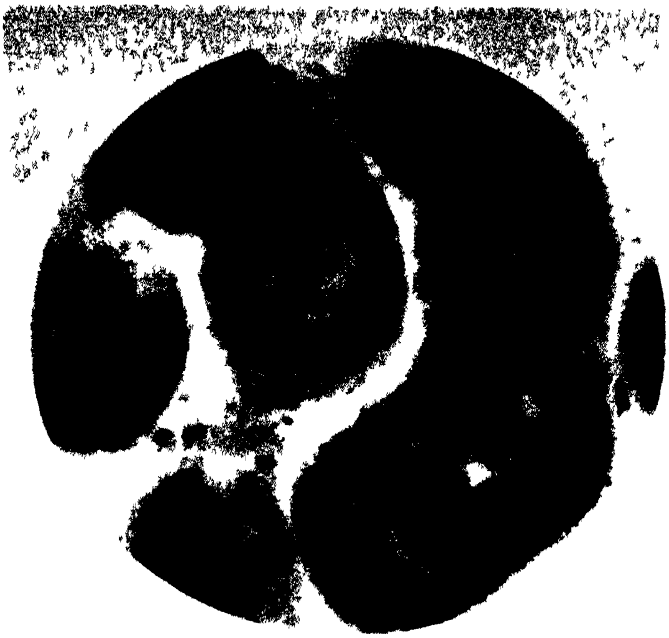

FIG. 91. Cloudy swelling. Convoluted tubules of kidney showing disappearance of normal rods owing to mitochondria becoming disarranged and forming into irregular masses. Bichromate method of Lorrain Smith and T Rettie × 900

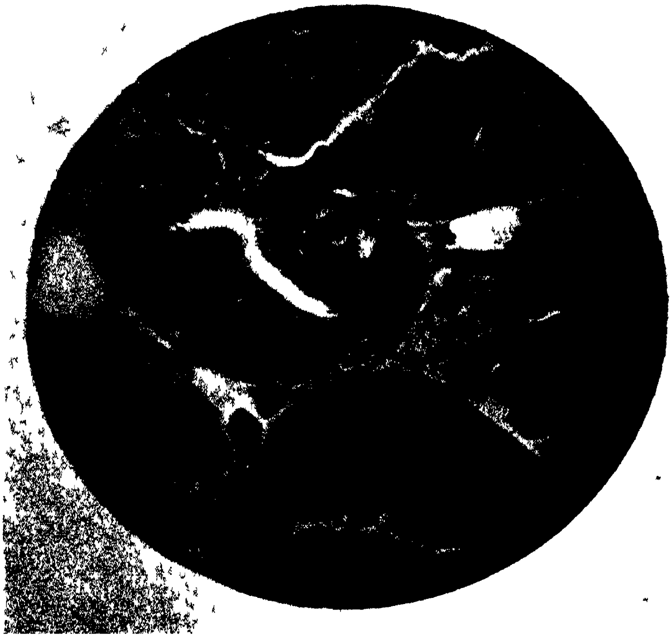

FIG. 92. Cloudy swelling. Convoluted tubules of kidney showing irregular size and grouping of mitochondria which have taken on the eosin stain and appear as dark granules. Hæmatoxylin and eosin. (By courtesy of Dr R F. Ogilvie and Editor of *Jour. Path. and Bact.*). × 1000.

rods tend to break into granules; as the process advances, such granules coalesce and form larger masses (Figs. 90, 91, 92). At this stage, early fatty changes may also be demonstrated (p. 198). The swelling is due to an alteration in the proteins of the cell, possibly a partial breaking-down to smaller molecules, whereby the osmotic pressure is raised within the cell. Often with this change within the cell there is a loosening of the intercellular substance or, where the cell is attached to a basement-membrane, it becomes free. Thus is produced the appearance described as **catarrhal change** (p. 41), where the cells in various stages of cloudy swelling, or even actually disintegrating, are seen lying free in the lumen, *e.g.*, of a bronchus or a renal tubule.

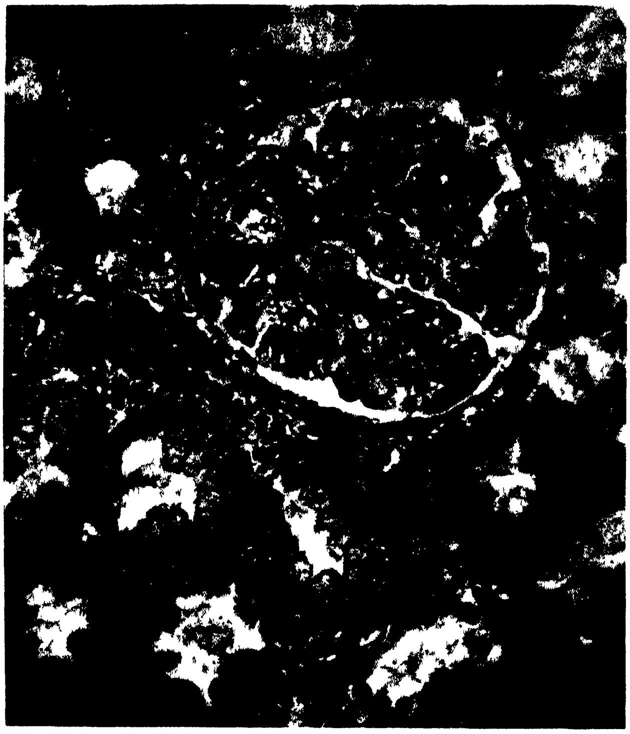

FIG. 93. Cloudy swelling of kidney. Convoluted tubules show stellate lumen, swelling and granularity of their cells. Intertubular capillaries are compressed. Hæmatoxylin and eosin. × 300.

Ætiology. Cloudy swelling is usually produced by the action of a **soluble toxic substance circulating in the blood,** especially bacterial toxins. Typical examples of cloudy swelling are seen in the acute infective fevers, *e.g.*, diphtheria, scarlet fever, pneumonia or typhoid, and in other infections and toxæmias. Organic poisons, *e.g.*, snake-venom, the vegetable poisons abrin and ricin, poisonous fungi, and many inorganic poisons, *e.g.*, corrosive sublimate, act similarly. As indicated above, the concentration of the toxin or poison determines its effects, for example, a strong solution of corrosive sublimate will produce immediate necrosis : and more dilute solutions cloudy swelling (Fig. 94) or even fatty changes. Excessive heat—hyperpyrexia—produces cloudy swelling, and changes in acid-base equilibrium also may be responsible for it.

As mentioned above, on p. 190, and on pp. 234–35, a similar appearance is seen in the earlier stages of post-mortem autolysis.

Organs and Tissues specially affected. Any cell may show cloudy swelling, but this change is noticeable particularly in organs rich in specialised cells, *e.g.*, liver, kidneys and heart. In these organs it is the more highly differentiated cells such as those of the liver as contrasted with those of the bile-ducts, and the convoluted-tubule cells rather than those of the collecting tubules of the kidney which show these degenerative changes.

Naked-eye Appearances. The organs affected are swollen, paler than usual and have a turbid " parboiled " or " cloudy " appearance. The cut surface bulges and often the structure is obscured because the swollen cells compress and empty the intervening blood-vessels. In the liver, the lobular outlines become indistinct. In the kidney, the cortex is relatively enlarged and pinkish-grey, while the redder pyramids stand out by contrast. The heart-muscle is paler than normal and becomes of a slightly-opaque, pinkish-brown colour.

FIG. 94. Kidney of rat showing effects of administration of a small dose of corrosive sublimate. There is complete necrosis of two ascending loops and a varying amount of cloudy swelling of the other tubules (By courtesy of Dr R F Ogilvie) Hæmatoxylin and eosin × 200.

The microscopical changes have already been indicated (p. 190) ; in the case of heart-muscle the striations may become obscured.

Course and Termination. The change may occur rapidly, *e.g.*, in six or eight hours in fever. Complete return to normal may follow removal of the agent causing the damage, but, if this damage is severe or if the agent continues to act, more serious forms of degeneration such as fatty changes or even complete disintegration and disappearance of the cell may ensue. Cloudy swelling is, therefore, to be regarded as merely a phase in cell-damage.

FATTY AND LIPOID CHANGES

For the details of the chemistry and metabolism of the fatty substances text-books of bio-chemistry and physiology must be consulted (a good résumé of the present position is given in " Applied Physiology " by Samson Wright, 7th edition, 1940).

The fatty substances that are of chief interest in pathology, as in physiology, are the neutral fats and certain lipoids.

The **Neutral Fats** are esters, chiefly of the higher fatty acids—oleic, palmitic, stearic—with the tri-hydric alcohol glycerol. Of these, oleic acid belongs to the unsaturated series, and its ester, tri-olein, is liquid at body-temperature and forms a large proportion of the neutral fat of the body. Tri-palmitin and tri-stearin are saturated fats and have a higher melting-point.

The **Lipoids** form a rather indefinite group of substances, the only common feature being their solubility in fat-solvents. Some, especially cholesterol and its esters, are anisotropic, *i.e.*, doubly refractive. **Lecithin** is a lipoid present in most tissues. It is a phospholipin, or phosphatid, containing nitrogen and phosphorus. Structurally it is composed of glycerol combined with one molecule each of oleic, palmitic and phosphoric acids plus cholin— a nitrogenous base. It can absorb water, becoming swollen and giving rise to " myelin-figures." In the brain are found **cerebrosides** in which the fatty acid is linked to a nitrogenous base which is united to a hexose sugar. They contain nitrogen but no phosphorus. **Cholesterol** is a monohydric alcohol and can thus form esters with fatty acids, and it is at the same time a lipoid, in that it dissolves in fat-solvents and is insoluble in water; but it and its combinations can form emulsions with water, and it is thus of importance in regulating the amount of fluid in cells. It is widely distributed and a frequent constituent of degenerated areas. It occurs almost pure in some gall-stones.

Fats and some lipoids may be hydrolysed and form soaps.

In the case of neutral fats, the potassium- and sodium-soaps are soluble, whilst the calcium-soap is insoluble. An example of pathological hydrolysis is that seen in " fat-necrosis " where the pancreatic enzyme is set free and acts on the adjacent neutral fat to form first fatty acids and finally insoluble calcium- and magnesium-soaps giving the appearance of white patches.

Fats are ingested in foodstuffs as neutral fat. In the intestine hydrolysis takes place and the fat is absorbed, mainly as soaps, partly as fatty acid; the process is greatly facilitated by the presence of bile. Re-synthesis of fatty acids with glycerol occurs in the cells of the intestinal mucous membrane, so that the lacteals contain mainly neutral fat. Transportation occurs by the lacteal system to the blood— in which the fat is present as an extremely fine emulsion— and by the blood it is carried to the cells of the body. A small amount of fat may perhaps be absorbed directly into the blood from the intestine. Part is stored as neutral fat in the storage-areas as depot-fat. It is the " *élément variable* " and has a lower iodine-value (*i.e.*, less unsaturation) than the " *élément constant*," which is the fat which is built up into the cells and forms an essential element of the cell-constitution. This " tissue-fat " has a higher iodine-value (*i.e.*, greater unsaturation) and is more labile than the depot-fat; it consists mainly of lipoids—lecithin and cholesterol esters.

The liver is intimately concerned with the preparation of fat for tissue-purposes. It desaturates the neutral depot-fats as they are brought to it and probably adds phosphoric acid and nitrogenous bases to form phospholipins which are then conveyed to and built up into the cell-protoplasm in combination with proteins. The more unsaturated a fat, the more unstable it is and the more readily oxidised. " The body stores its powder wet for safety (depot-fat) and dries it only when required for use (tissue-fat)." [1]

Normally, fat can be recovered chemically from most tissues, but it is possible to show it by histological staining methods only in certain areas such as in adipose tissue (depot-fat), suprarenal (lipoids), and occasionally to a small extent in liver.

The grey annular opacity known as the " arcus senilis," seen round the periphery of the cornea in many elderly people, is produced by the presence of intracellular globules of fat. It is *not* necessarily due to arterio-sclerosis, and can be artificially induced in animals by feeding them on a diet rich in cholesterol. It is apparently of little or no clinical significance

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[1] Leathes and Raper, " The Fats," 2nd ed., 1925.

In pathological conditions, fat may **become apparent** histologically in practically any cell or tissue (p. 198), and this abnormal "appearance"—*i e*, manifestation or becoming-visible—of fat is described as an infiltration or a degeneration.

There has been much controversy as to the nature of the fatty changes seen in pathological conditions, and the terms "infiltration" and "degeneration" have been used as alternatives by various authors with some resulting confusion of the issue. There are certain difficulties in applying them, but each term has its use.

Fatty Infiltration. This term may be used to denote an accumulation of fat in a situation where fat is usually stored, or in cells which are still functioning. The most obvious example is that of **Obesity** or **Adiposity,** where an excess of fat is laid down in the normal fat-depots such as the subcutaneous tissues, the omentum and peri-nephric tissue. This accumulation may be due partly to excess intake of food-fat, but often is due to **endocrine** disturbances causing altered metabolism. Disturbance of function of the **pituitary** and of the **hypothalamic nuclei** of the brain may lead to a form of obesity (p. 810: and Fig. 595, p. 989).

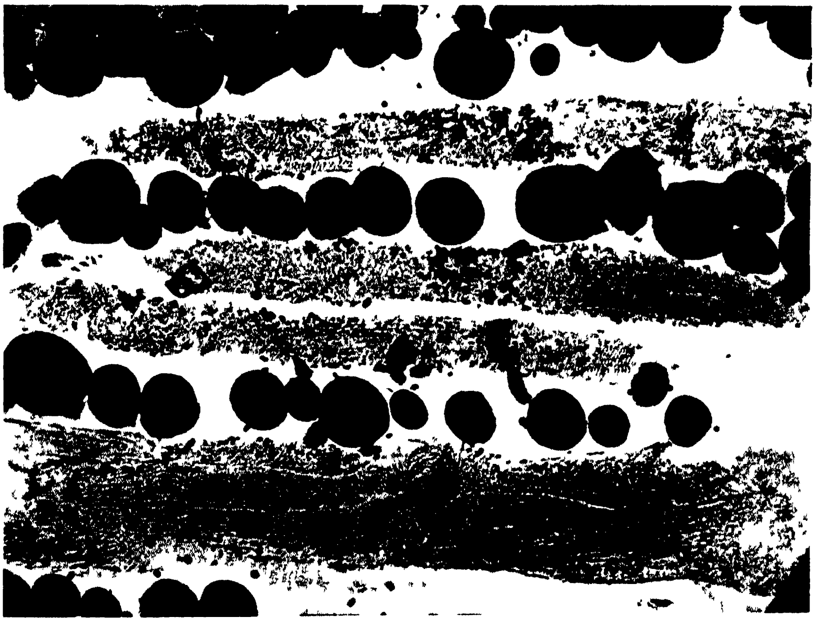

FIG. 95. Fatty infiltration of skeletal muscle (erector spinæ) occurring in pseudo-hypertrophic muscular atrophy (pp 1243–4). Stained with osmic acid. × 200

Castration may be followed by a laying on of fat—an occurrence of which advantage is taken in the fattening of live-stock.

After **pregnancy,** during **lactation** or at the **menopause,** women often become obese, because of **endocrine** influence, and analogous changes also occur in men. In cases of diminished functional activity of the **thyroid,** obesity may be developed and be removed by giving thyroid hormone (p. 833).

Ogilvie[1] has shown that in obese people the islet-tissue of the pancreas may be increased.

Sometimes fatty infiltration is local and due to atrophy of adjacent tissue, *e.g.*, in **skeletal muscle** atrophied from disuse or disease there may be an excess of fatty tissue between and replacing the atrophic muscle-fibres (Fig. 95 : and Fig. 754, p. 1173). Similarly in and around the atrophying **thymus** there develops an excess of fat, and an atrophic contracted kidney may have an excess of fat about it. In the **heart** there may be increase of surface fat with extension between the muscle-fibres, especially of the right ventricle, and associated usually with some atrophy of these muscle-fibres (*see* Fig. 96).

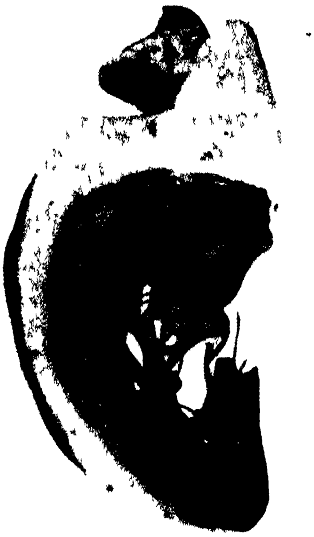

FIG. 96. Fatty infiltration of myocardium of right ventricle of heart. The muscular fibres are separated and almost completely replaced by fat. There is also a thick layer of subepicardial fat.

The **liver** is an organ which normally has to deal with the fat brought to it for desaturation, etc., and it may show an excess, or infiltration, of fat in its cells. Frequently this is associated with damage to the liver-cells, and this condition will be considered under fatty degeneration.

Fatty Degeneration. This term indicates an interference with the function of the cell or tissue as a result of which fat becomes visible histologically as granules or globules in the cell or tissue. Such change may occur in any cell and may result from diverse causes. It may be accompanied by an accumulation of fat : that is to say, infiltration and degeneration may occur together; but in such case, were it not for the cell-damage, *i.e.*, the degeneration, the fatty infiltration would not appear.

Fatty degeneration, the term being used as defined above, may occur **physiologically** in the various senile changes associated with advancing age ; or it may occur at any period of life where there is **diminished functional activity,** as in unused or in paralysed muscles.

Defective nutrition, or **defective oxygenation,** may cause it. If general, as in old age, starvation, cachectic conditions and severe anæmias, many organs may show it in their cells. Local interference with nutrition or oxygenation, as in arrest of blood-supply to a part, may lead to its production, as in the case of infarcts, tumours, or patches of degeneration in blood-vessels.

Fatty degeneration has already been mentioned in connection with cloudy swelling and the same causes are responsible for both. It may accompany other degenerative processes such as amyloid degeneration.

Bacterial toxins, such as those of diphtheria bacilli or of the virulent pyogenic cocci, may produce the condition. It is often pronounced in chronic infections, *e.g.*, in tuberculosis.

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[1] R. F. Ogilvie, *Jour. Path. and Bact.*, 1933, **37**, 473.

Some **organic poisons** are responsible for severe fatty degeneration. Of these, **chloroform** is important, especially if combined with a bacterial infection. Delayed chloroform-poisoning is liable to occur in such cases if chloroform be used as an anæsthetic, and one feature is the marked fatty change in the liver, kidneys and heart-muscle, and, microscopically, in many endothelial cells of the capillaries. Other organic substances which, in toxic doses, may cause the change are alcohol, iodoform and carbon monoxide.

Inorganic poisons are also important in this connection, especially phosphorus, arsenic, antimony and mercury. Of these, **phosphorus** has been used in the experimental study of fatty changes ; and phosphorus-poisoning has now been described as due to tracer-bullets remaining embedded in the tissues, and also to the use by the Germans of explosive machine-gun bullets, each actually containing 10 grammes of phosphorus.[1]

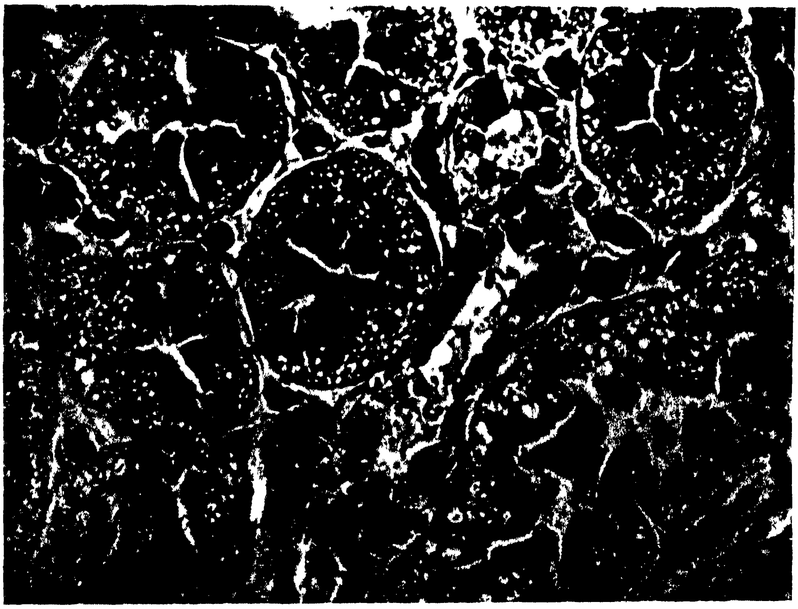

FIG. 97. Fatty degeneration of epithelial cells of convoluted tubules of kidney. The clear areas represent the position from which the fat-globules have been dissolved out in the process of embedding in paraffin for section. × 450.

An extreme degree of fatty degeneration is seen in **Addisonian anæmia** (p. 646 *et seq.*). This is to be explained by reduction of oxygen-carrying power of the blood and consequent **anoxæmia** which damages the cells (p. 157).

In the metabolic disturbance of **diabetes mellitus,** in addition to the inability to utilise sugar, fat is incompletely oxidised, producing ketosis from abnormal acid-radicles (p. 800 *et seq.*). Fat may also accumulate in the blood, giving rise to **lipæmia** and, in a marked case, showing in the drawn blood as a creamy emulsion of fat which rises to the top on standing. In this condition the organs may show marked fatty changes and fat be present in the sinus-system of the lymph-nodes and in the spleen-pulp.

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[1] "German Explosive Bullets," by J. R. F. Popplewell, *Brit. Med. Jour.*, 1943, *i*, 111.

In **autolysis** of dead tissues such as infarcts, fat may appear, and is derived from the disintegrating cells.

Mechanism of Fatty Change. If normal heart-muscle be examined microscopically, no fat will be demonstrated within the muscle-cells by ordinary fat-staining methods. If the same methods are applied to heart-muscle in the condition of fatty degeneration, numerous fine granules or globules of fat are visible. Yet chemical analysis of both normal and " fatty " hearts may show practically the same amounts of total fat. The same phenomenon is found in the case of normal and " fatty " kidney. The fat has become visible. In its previously tightly-bound condition the fat is known as " masked " fat. It is fat which has been firmly linked with the proteins of the cell and has then become separated off or " unmasked " by the damage to the cell. The term " phanerosis " is employed for this " becoming visible " of the now stainable fat (*cf.* p. 195). As before stated, it is in relation to the mitochondria that such fatty particles first make their appearance in the cytoplasm (pp. 190–2).

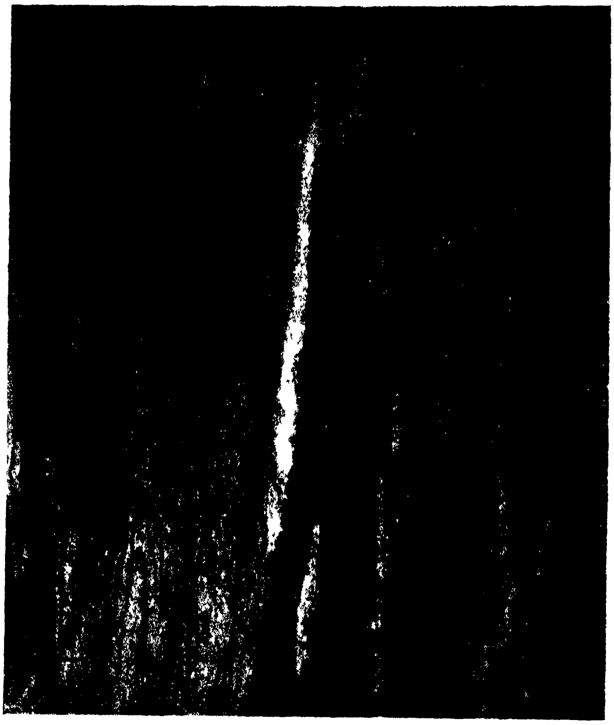

FIG. 98. Fatty degeneration of heart-muscle. Fat is stained black by osmic acid and appears as small droplets within the heart-muscle fibres. × 300.

In an attempt to identify the source of this " unmasked " fat much experimental work has been done, the earliest being that of Lebedev, followed by Rosenfeld and others. Much of their work was done on dogs, phosphorus being used as the damaging-agent and the fatty changes found in the liver being investigated. As the liver itself is an organ intimately concerned with the metabolism of fat, it is, as regards its fatty changes, in a rather different category from organs such as kidney or heart.

In the **liver** of an animal which has been poisoned by phosphorus, much fatty change is seen histologically. Chemically there is also found a decided increase of fat. But, if the animal has been starved previously so as to empty all its depot-fat (*élément variable*), and then poisoned, no ordinary fatty degeneration is seen—though minute droplets of " myelin-substance " may be shown microscopically. Again, if a dog be fed with mutton-fat, its depot-fat resembles this fat and, when poisoned with phosphorus, the fat found in its liver also has the general characters of mutton-fat. From such experiments it has been concluded that the condition is one of " infiltration " rather than of " degeneration." But what has happened is that the poison, phosphorus, has interfered with the function of the liver-cells, which have constantly to deal with depot-fat brought to them for treatment and distribution to the body-tissues in altered form. The result of this interference is that the liver-cells cannot deal with the fat brought to them. Thus in a sense there is an " infiltration," but the fact that the fat has become stainable indicates a break in the fat-protein combine in the cell, that is, the cell is damaged and the resulting fat is a product of degeneration.

In the case of the **kidney** or **heart-muscle** there may, or may not, in fatty degeneration, be an increase of the total fat, estimated chemically. Fat reaches these organs after treatment in the liver and is bound up with the protein in their cells. The same " unmasking " occurs as the result of damage by noxious agents, and, if fat is being circulated in the blood in sufficient amount, some may also accumulate in the cells of these organs, though not to the extent seen in the liver. Here again, the essential factor is the injury to the cell, causing its degeneration, with appearance of stainable fat, in short—fatty degeneration.

Course and Result of Fatty Degeneration. The length of time required for the production of fatty degeneration varies greatly. The condition may be produced in a few hours, for example by intense septic poisoning. In other cases it may take days. If the cause be removed in time and the damage to the cells has not been too severe, recovery, complete or partial, will occur ; or, the process may go on to necrosis of the cell. The possibilities are the same as those already mentioned in the case of cloudy swelling. If the individual survives, and the damage is local, there may follow absorption, total or partial, of the dead cells and fatty debris ; or the area may, with or without calcification of this debris, become encapsulated. Forming part of the debris and remaining unaltered, there may often be found cholesterol or cholesterol-esters of the fatty acids. These may be demonstrated in suitable histological preparations, or in ordinary paraffin-sections they may show as the characteristic " cholesterol-clefts " (*see also* pp. 201–3).

Distribution, Naked-eye and Microscopical Appearances. The same types of cell as in cloudy swelling are affected, and the same organs show the change naked-eye, viz., those with large numbers of highly-specialised cells such as the **liver, kidney** and **heart**. The organ may be normal in size or slightly swollen. If there is much fat present, as in the liver, the organ may be definitely enlarged. In colour, the fatty areas vary from a pale-, or greyish-, to a bright, almost canary-yellow. The organ is often softer than normal, sometimes actually friable, and it may be greasy in appearance and to touch.

The **distribution** in different organs varies. In the **liver,** it may be diffuse, giving the organ a uniform yellow appearance ; or it may be more pronounced either at the periphery or at the centres of the lobules. In the **kidney,** the cortex is most affected. In the **heart,** the left ventricle usually shows the change more markedly than the right and often in its inner layers only ; whilst the distribution of fat may be uniform, giving the muscle a pale brown or yellow appearance, more commonly it is patchy and shows as yellow mottling on a browner background—the so-called " thrush-breast " or " tabby-cat " appearance (p. 652). Sometimes, in the case of pericarditis, a layer of fatty myocardium, 1 or 2 mm. thick, can be seen immediately beneath the inflamed serous coat.

The appearances of the fatty changes seen in **atheromatous blood-vessels** are described later (p. 201).

Microscopical Appearances. When associated with cloudy swelling, the affected cell may be enlarged ; otherwise it may be of normal size, smaller than normal, or even shrunken. The nucleus may be unaffected, or, if the damage has been severe, it may show degenerative changes such as pyknosis, karyorrhexis or karyolysis (Fig. 3, p. 14). The fatty particles at first are minute and related to the mitochondria, they then tend to enlarge and coalesce into droplets of varying size (*cf.* Figs. 90–2, pp. 190–1, and Plate IX, opposite).

In the **kidney,** it is especially the cells of the convoluted type of tubule that are affected, and the fatty droplets are often aggregated towards the outer or more peripheral parts of the cells (Plate IX, opposite, Fig. 2). In severe cases, the collecting tubules may be affected, though to a lesser degree, and in certain cases the cells of Bowman's capsule and the endothelium of the glomerular capillaries may show the change. In the **heart,** the affected fibres show fine granules or droplets of fat in parallel rows arranged along the fibrils (Fig. 98, p. 198). In the **liver,** the distribution and character of the changes vary. Where there is much infiltration—as previously described (p. 198 *et passim*)—all the cells of the lobule may be distended with fat and resemble adipose tissue rather than liver. This is well seen in some cases of chronic alcoholism. In other instances, such accumulation is confined to the more peripheral cells of the lobule, as in chronic venous congestion. In more acute toxic conditions, or in poisoning by phosphorus or chloroform, the change is irregular, sometimes more pronounced in the cells toward the centre, sometimes diffuse in the cells throughout the entire lobule. The fat-globules are often small and numerous, though all gradations can be seen, from many small to fewer large globules. (Plate IX, Figs. 1 and 3, opposite).

Fatty degeneration in the cells of other organs and tissues has the same general characters, but can be recognised only on microscopical examination, as such cells are not aggregated as are those of the above-mentioned organs, *e.g.*, in the brain, in certain conditions, many nerve-cells may show fat-globules, but this is not apparent macroscopically. It must be remembered that phagocytes may be loaded with fat or lipoid material which they have ingested. Such cells are merely going about their business as scavengers and are in no sense examples of the above-described fatty changes. Cells of this nature may be seen in the neighbourhood of a necrotic focus, *e.g.*, an infarct, where they are in process of removing the fatty debris of cells which

DESCRIPTION OF PLATE IX

PLATE IX

FIG. 1. *Fatty Infiltration of Liver.* Frozen section stained with scarlet red and hæmatin. The fat is seen in the form of large globules contained in, and distending, the liver-cells towards the periphery, of the lobules. × 40

FIG. 2. *Fatty Degeneration of Kidney.* Frozen section stained with nile blue (Lorrain Smith's method). Numerous small, discrete, fatty globules and particles are shown in the cells of the secreting tubules, more especially towards their outer parts, *i.e.*, next the basement-membrane. × 300

FIG. 3. *Fatty Degeneration of Liver* from a case of delayed chloroform-poisoning. Frozen section stained with sudan III and hæmatin. The fatty material is stained a reddish-orange colour, and is arranged in smaller particles towards the centre of the lobule (lower part of section), where the cells show considerable atrophy. The fat towards the periphery is in larger globules which distend the cells. The capillaries between the columns of liver-cells show chronic venous congestion. At the upper margin of the figure is seen a portion of a portal tract, with sections of a bile-duct, hepatic artery, and part of a portal vein. × 200

FIG. 4. *Atheroma of Aorta.* Frozen section stained with sudan III and hæmatin. Towards the lumen of the vessel (upper margin of section) is seen the laminated thickening of the inner coat. As this is traced outwards, the fatty material increases in amount till, towards the middle coat, it is contained in large spaces, which also contain calcareous particles stained dark blue with hæmatin The internal elastic lamina has undergone degeneration and fragmentation The middle coat shows slight degenera tive changes towards its inner part Outer coat is not specially affected × 40

PLATE IX, p 200.

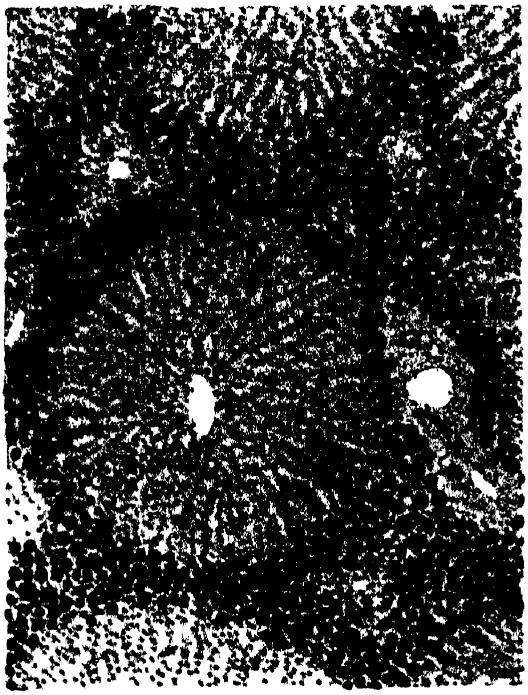

Fig. 1 × 40

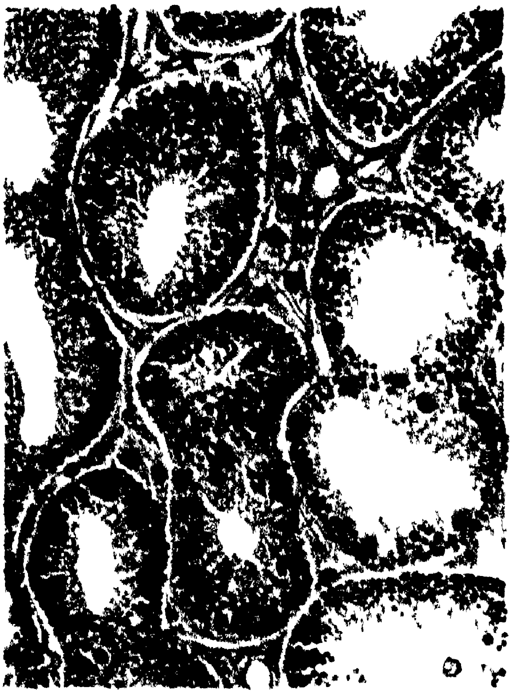

Fig. 2 × 300

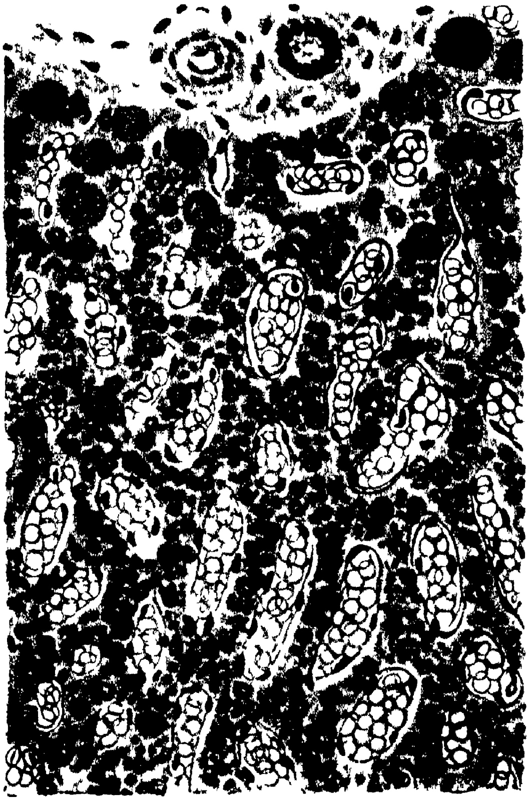

Fig. 3 × 200

Fig. 4 × 40

have disintegrated. They are also present, often in large numbers, round an abscess. In the central nervous system, fatty material from degenerated myelin is taken up by similar cells which collect along the perivascular spaces and elsewhere (Figs. 645, 659–660, and 749, pp. 1056, 1084–5 and 1161).

In the **fatty streaks** seen in arteries, the fat is in the form of globules in the sub-endothelial cells, some of which are wandering phagocytes and some of fibroblastic type. In **atheroma,** the fat is in similar cells and also lies free, frequently mixed with calcareous granules. There is often a large admixture of cholesterol in such deposits (Plate IX, Fig. 4, opposite).

Chemical and Staining Reactions. The histological methods used to demonstrate fat in the cells or tissues depend on (1) the physical characters of the fatty substances, or (2) on chemical union of the reagents with these substances.

Under (1) come the common stains for fat, *sudan III* and *scarlet-red*, which colour neutral fats a brilliant yellow- or orange-red because they are themselves soluble in fat. *Nile blue sulphate A*, introduced by Lorrain Smith (1907), contains a red substance (oxazone) which, like *sudan III* or *scarlet-red*, dissolves in neutral fat and thus tints it red or pink ; in addition it has a blue basic substance (oxazine base) which combines with fatty acid to give a deep blue colour. (*See* Plate IX, Fig. 2.) It is now difficult to obtain samples of nile blue (or "nile pink," as Rettie calls it) of the same composition as originally used, and the pink staining of neutral fat is poor or absent with the ordinary nile blue now available. Rettie has described a method of preparing "nile pink" which acts as in the original method.[1] By means of this method, most of the fat seen in the common variety of degeneration is in the form of neutral fat.

Another physical method of investigation is by means of the **polarising microscope.** This is applicable only to certain fats and lipoids which are optically active. Lecithin and cholesterol and their compounds may be recognised by their rotation of polarised light (Fig. 99, p. 202) and by estimating the melting-point of their crystals on a hot stage.

Under (2) are to be considered such methods as the following :—

Osmic Acid (OsO_4) acts by oxidising the fat and forming an insoluble black compound with it. It will, therefore, stain only an unsaturated fat such as olein—not palmitin or stearin. The stain will demonstrate fatty degeneration in the heart, liver or kidney ; and it also stains myelin of nerves, both normal and degenerated. **Marchi's Method** is one of selective oxidation and its main use is in demonstrating recent degeneration of the myelin of nerves. Bichromate of potassium is first applied and oxidises the labile and easily oxidisable normal myelin : osmic acid is then applied and can act only on the more stable, less easily oxidised, degenerated myelin which, being unsaturated, shows up black. **Weigert's Method** employs the same principle of selective oxidation plus staining with hæmatoxylin. During oxidation the chromic acid combines with the oleic acid of the fat and these form an insoluble lake with the hæmatoxylin. If such "chroming" is carried too far, over-oxidation occurs and the hæmatoxylin will not stain. While this method is also used mainly for nerve-degeneration it can be applied to any unsaturated fat. The practical details of these methods can be mastered only by actual laboratory work ; but examples of their use will be found in the illustrations in Chapter XXVIII on the Nervous System.

Chemical methods used for the estimation of total fats, lipoids and soaps are those in use in bio-chemistry and need not be detailed here.

Fats and lipoids, being soluble in chloroform, benzole, xylol, ether, etc., are readily dissolved from sections of tissues prepared by paraffin-embedding, and the spaces occupied by the fat-globules appear as clear areas in the section. A similar phenomenon occurs where crystals of cholesterol have been present in a tissue, the spaces left being known as "cholesterol-clefts" (*see* p. 199).

By such chemical and histological methods the fats demonstrated in fatty degeneration are largely neutral fats, mainly unsaturated, with variable admixtures with lipoids, to which reference has already been made (p. 194).

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[1] See *Jour. Path. and Bact.*, 1931, **34**, 595.

LIPOID CHANGES. In ordinary fatty degeneration, lipoids may occur, together with neutral fats, but usually in relatively small amounts. In some conditions, however, the lipoid content of the affected part is high. There may be an associated increase of lipoid in the blood—mainly in the form of cholesterol-ester.

Cholesterolæmia. Normal blood contains about 0·16 to 0·25 per cent. (160 to 250 mgr. per 100 c.cm.) of cholesterol. This amount is but little affected, even by a cholesterol-rich diet. In **pregnancy** there is a distinct increase (up to 0·45 per cent. or 450 mgr.) but this is reduced again to normal during lactation. There is an increase in **arteriosclerosis,** especially with hypertension : in **diabetes** : and in the tubular or " parenchymatous " type of **nephritis** (nephrosis), in which very high figures may be found (up to 1·2 per cent.). In the last-mentioned condition, the cortex of the kidney is mottled or streaked with light-yellow markings which correspond to the tubular epithelium, the cells of which are loaded with doubly-refractile lipoid ; and there may be also casts containing lipoid in the tubules. The renal accumulation of cholesterol is due probably to the lipoid being taken up from the glomerular filtrate and becoming concentrated in the tubules, which may also be damaged. Excess of blood-cholesterol occurs in some cases of jaundice with **gall-stones** (*cf.* p. 788) : in chronic alcoholism : and in some mental conditions.

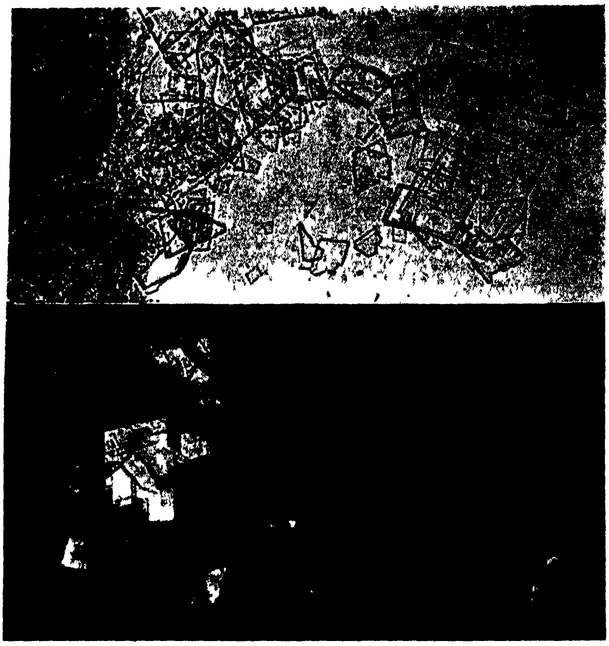

FIG. 99. Cholesterol-crystals from the contents of an old-standing hæmorrhagic cyst of thyroid. In the upper field numerous characteristic plates of cholesterol are seen, some broken, some mixed with blood-debris. In the lower field these plates appear doubly refractile when examined by polarised light. × 85.

The cause of cholesterolæmia is, in many cases, obscure. In diabetes, it is due probably to the disturbance of fat-metabolism accompanying the carbohydrate upset, and it may be removed by treatment with insulin. In the form

associated with renal disease, there is also loss of plasma-protein and general malnutrition ; and undue fat-mobilisation may be regarded as an attempt to correct this. The occurrence of cholesterolæmia in starvation would suggest some such explanation.

Lipoids, largely as cholesterol-esters, may be found (together with fats) in the degenerated patches in the inner coats of arteries in **atheroma** (*see* p. 485). At the site of **old hæmorrhages** or in **old necrotic tissue,** crystals of cholesterol are to be found (pp. 199 and 201). In **old cysts,** especially if lined by stratified squamous epithelium, the liquid or often the inspissated contents may glisten from abundance of this lipoid (Fig. 99). In **gall-stones,** cholesterol is always present in greater or less amount, sometimes almost pure, forming a white calculus of wax-like consistence.

Cholesterol, alone or with other lipoids, occurs in excess in reticulo-endothelial cells in certain rare conditions—in xanthoma as yellow nodules : in the enlarged spleen of the diseases named after Gaucher, Niemann-Pick, and Dyke respectively (*cf.* pp. 689 and 700), and in the lipoidoses of the central nervous system (pp. 1071–2).

Adipocere. When a dead body has been in water or damp earth or peat for at least some weeks, the body-tissues may become transformed into a solid wax-like substance called adipocere. Chemically this consists mainly of insoluble fatty acids or soaps. This formation is of some medico-legal importance.

THE MUCINOID (MUCOID AND COLLOID) DEGENERATIONS

MUCOID AND COLLOID DEGENERATIONS are by many authorities considered separately. It is convenient to class them together under the common name of **Mucinoid Degeneration,** as suggested by Greenfield and Lyon.[1] The term " colloid," used in relation to degenerative change, is better kept as a morphological descriptive term for naked-eye or microscopical appearances without reference to any chemical implication. Frequently, it is used to describe an inspissated firm material, as in " thyroid colloid " or " colloid casts " in the kidney, or " colloid carcinoma " ; all of which differ greatly in chemical composition, but have a somewhat similar physical appearance. The colloid appearance is often due to the material being in a confined space and losing water, and so becoming, as the term implies, glue-like in consistence. " Colloid," therefore, may be formed from various mucins and even from proteins such as serum-globulin, serum-albumin and nucleo-protein. In many cases " hyaline " (*see* p. 214) is an equally appropriate term.

The **Mucins** are complex protein substances containing a carbohydrate-radicle, *i.e.*, they are gluco-proteins. They are the cause of the sliminess of the mucous secretions of the respiratory and alimentary tracts ; and substances closely allied to them are found in the urine (a mucinoid) and bile (a mucinoid nucleo-albumin). The mucins are also closely allied to the mucinoids or mucoids found normally in the connective tissues.

Mucin, if dried, swells again on the addition of water, and forms " mucilage," which is soluble only with difficulty. On the addition of acetic acid it is precipitated in the form of a tough adhesive curd, insoluble in excess of acetic, but easily soluble in excess of hydrochloric, acid. It is not coagulated on boiling, and is readily soluble in alkalies. By alcohol it is not precipitated unless in the presence of a sufficient quantity of neutral salts, in the absence of which only a pale opalescence is produced. It is precipitated by copper sulphate, mercuric and ferric chlorides, and lead acetate, but not by tannin or potassium ferrocyanide. In sections, it is stained a bright pink colour with Mayer's mucicarmine, and the demonstration of its presence is sometimes of differential diagnostic value, *e.g.*, in the identification of some metastatic bronchial carcinomatous tumours, say in the brain, in which mucin is frequently present, whilst it is not found in tumours of similar appearance but which are secondary to mammary cancer (Figs. 735 and 736, p. 1147).

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[1] W. S. Greenfield and G. Lyon, "Chapters in Pathology," Edinburgh, 1905, p. 15.

The **Pseudomucins,** also gluco-protein substances closely allied to the mucins, are found in the contents of certain cysts, especially of the ovary. They are freely soluble in water, and are *not* precipitated by acetic acid or by the mineral acids. Alcohol produces with them a tough curd-like precipitate, but otherwise they react very much like true mucins. The **Paramucins,** also members of the gluco-protein group, and found sometimes in the form of a clear "trembling jelly" in ovarian and other cysts, are insoluble in water, and, except for the fact that they are precipitated by tannin, react like the mucins.

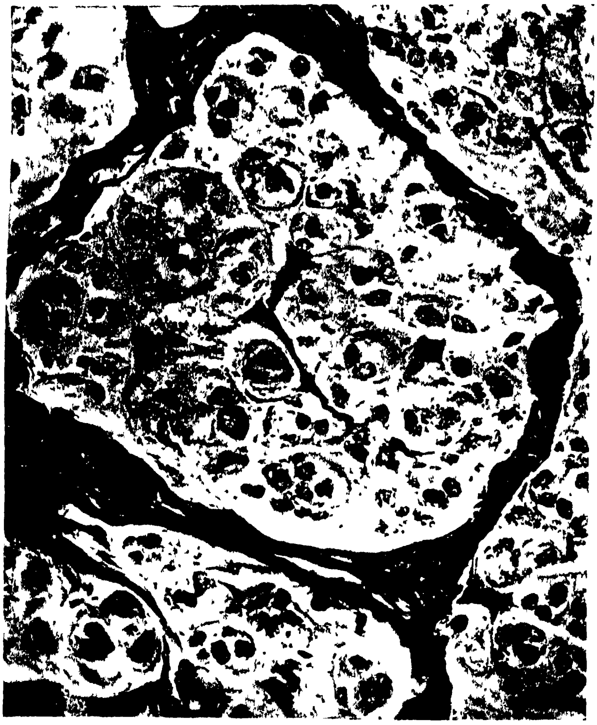

FIG. 100. Mucinoid degeneration of cells in "colloid" cancer. × 200.

The **Mucoids** or **Mucinoids** of connective tissue are precipitated by acids, and are soluble in dilute alkalies. They do not give any precipitate with tannin. They are gluco-proteins, and do not differ essentially from the mucins except by the possession of a higher sulphur-content. Members of this group are found in tendon, bone and cartilage, and in certain of the body-fluids.

The reducing carbohydrate yielded by all these substances as a result of hydrolysis with dilute mineral acids, contains nitrogen, and is either glucosamin or a closely-allied substance.

The degenerations are best studied in two groups, as follows :—

I. Mucinoid Degeneration of Cells.
II. Mucinoid (or " Myxomatous ") Degeneration of Connective Tissues.

I. MUCINOID DEGENERATION OF CELLS

Mucin is normally secreted by the " goblet- " or " chalice-cells " of mucous membranes and by the cells of mucous glands, in the cytoplasm of which it first becomes visible as the so-called mucigen " secretion-granules." Towards the free end of the cell these gradually swell and coalesce to form a clear, transparent, colloid or jelly-like substance, which distends the cytoplasm next the lumen. It is then secreted, there being in this physiological process no disintegration of the cyto-reticulum or injury to the vitality of the cell.

A pathological exaggeration of this process may be found in certain mucus-secreting cells, for example in catarrhal inflammation of mucous membranes, in which there occurs a series of changes similar to those of cloudy swelling. Analogous changes may occur in other glandular epithelial cells, for example in those of the kidney or thyroid, or in epithelial tumour-cells, *e.g.*, in cancers growing from the stomach, intestine, breast, etc., (Fig. 100 opposite, and Fig. 189, p. 349), or in compound cystic ovarian adenomas. Its presence in the cells of chordomas (tumours arising from remains of the notochord, *see* p. 306) is so characteristic that they were named " physaliphorous cells " by Virchow (Figs. 140–1, p. 307). Cells undergoing mucoid or mucinoid degeneration tend to swell into a clear, soft, jelly-like mass containing mucin, pseudo-mucin, or paramucin. If secreted into a closed cavity, these substances will accumulate ; if on a free surface, there will be increased flow of secretion. In this pathological process, unlike what occurs in the case of the physiological secretion of the mucin, the cytoplasm of the cells tends to disintegrate, the intercellular cement-substance to undergo solution, and the cells themselves to pass into and blend with the secretion—a process also well seen in the so-called colloid forms of the degeneration.

II. MUCINOID (OR " MYXOMATOUS ") DEGENERATION OF CONNECTIVE TISSUES

As already mentioned, the connective tissues normally contain certain members of the gluco-protein series.

In the fœtus, mucoid or mucinoid connective tissue is the normal precursor of all the connective tissues, and it is found also in the umbilical cord (" Wharton's jelly "). It is formed of stellate, or somewhat irregular, cells, with long branching and interlacing processes, lying in a clear homogeneous or slightly granular semi-fluid matrix containing mucin or mucinoid substances. The only tissues which in the adult body normally retain their resemblance to the original mucinoid tissue are the vitreous humour of the eye and the pulp of the teeth.

Pathologically, a similar appearance may be found as a retrogressive process occurring in any of the connective tissues. A characteristic form of such mucinoid degeneration may occur in the bone-marrow of old and debilitated patients, and also earlier in life in certain cases of acute or chronic disease, especially in alcoholic subjects, in which that tissue has become exhausted (p. 608). The blood-forming elements disappear, and the fat of the adipose tissue is absorbed, the cytoplasm of the fat-cells being transformed—from the periphery of the cell inwards, as the fat disappears—into a fibrillated or in some instances a somewhat denser homogeneous gelatinous or mucinoid substance, which becomes fused with that formed from neighbouring cells. The process may also occur in cartilage or in the bones of old people, especially if these tissues are undergoing rapid absorption.

In myxœdema—a condition due to atrophy of the thyroid gland (p. 835)—a widespread form of mucinoid degeneration supervenes in the connective tissues. The condition here is due to defective nutrition and interference with both the formative and the absorptive processes, which in the normal state to a large extent depend upon the influence of substances secreted by the thyroid. Mucinoid (" myxomatous ") degeneration is not infrequently seen in various inflammatory conditions, for example, in granulation-tissue, and in the so-called " mucous polypi " growing from the mucous membranes of the nose or nasopharynx, intestine, etc. These latter are often described as myxomatous " tumours," but they are in all probability mostly not true neoplasms, but rather to be regarded as chronic inflammatory overgrowths, which become polypoidal owing to the constant movements of the contents and walls of the passages into which they project, whereby they are dragged upon and tend to become elongated.

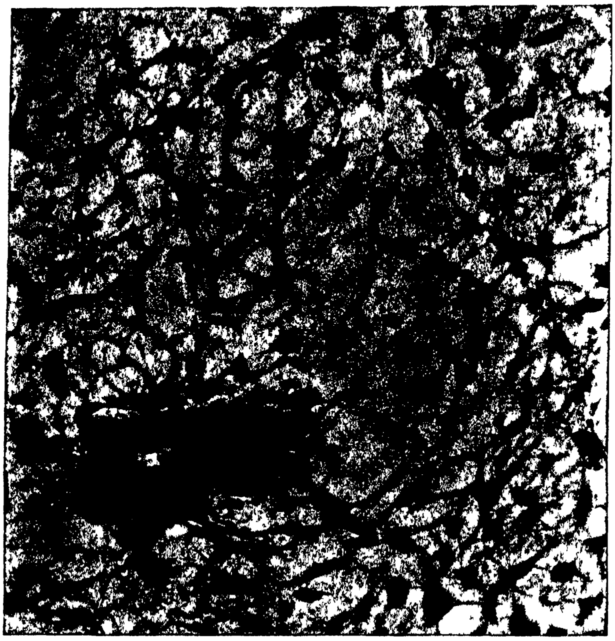

FIG. 101. Mucinoid (" myxomatous ") tumour of breast, showing characters of cells. × 250.

Mucinoid (" myxomatous ") degeneration occurring secondarily in tumours is comparatively common, for example in fibromas, chondromas, lipomas, carcinomas, sarcomas, etc. The so-called "hydatid mole" or myxoma of the chorion may, however, for the present at all events, be regarded as a true neoplasm or new growth (pp. 301–2 and 352).

The Changes produced in the Connective Tissues by Mucinoid ("Myxomatous") Degeneration. The tissues become transformed into a transparent or semi-transparent, more or less homogeneous, viscid substance of gelatinous or gummy consistency. **Microscopically,** the cells typical of the condition are irregularly stellate or triangular in outline, and possess long, delicate processes which branch and anastomose with one another. They have somewhat large, rounded or ovoid, faintly staining nuclei, poor in chromatin. The matrix or intercellular ground-substance may be homogeneous, slightly granular, or in some instances finely fibrillated, in structure, and varies greatly in its amount, the cells being sometimes widely separated, and in other cases more closely arranged. All intermediate stages between such a mucinoid (" myxomatous ") condition and fully formed connective tissue may be found (Fig. 101).

GLYCOGENOUS INFILTRATION

Glycogen or "**animal-starch**" is a member of the polysaccharose group of carbohydrates, having the formula $(C_6H_{10}O_5)_n$. It is found in most of the actively-functioning cells of the body, and especially in those of the liver and muscular tissue, but also, though to a less extent, in the cells of the kidney, cartilage, and epithelium generally, and in leucocytes. Pathologically, this substance may be increased in any of these situations, and it is found also in certain tumours. In some inflammatory conditions such as acute suppurative appendicitis, acute fevers (*e.g.* pneumonia), and in chronic infective diseases and cachexias, especially tuberculosis, there may be considerable increase of glycogen-granules in the cytoplasm of the circulating neutrophil leucocytes and in the blood-plasma (p. 597).

In diabetes mellitus, owing to insulin-deficiency and consequent lack of utilisation of glucose, the glycogen in the liver and skeletal muscle is greatly reduced or absent, while the heart-muscle still contains it. In the kidney, the cells of the convoluted tubules and the loops of Henle show excess of glycogen. Insulin-treatment may re-establish the normal distribution of glycogen, *i.e.*, will cause the disappearance of glycogen from the kidney-cells and its reappearance in the cells of liver and muscle. (*See also under* Diabetes Mellitus, p. 800.)

Von Gierke's Disease. Excess of glycogen occurs in the rare disease associated with the name of Von Gierke (1929). This disease is found in children and is characterised by an enormous accumulation of glycogen in the liver with great enlargement of that organ, the cells being distended with glycogen. The condition appears to be due to lack of the ferment which normally transforms glycogen to glucose. The kidneys (p. 858) and muscles may also contain excess of glycogen, and cases have been recorded where the heart has been greatly enlarged from distension of its muscle-fibres with glycogen.

Chemical Tests and Reactions. Glycogen is freely soluble in water, and forms a pale opalescent solution. In the tissues after death, it is rapidly converted by hydrolysis into glucose, and therefore, for microscopical examination, immediate fixation in alcohol, in which it is insoluble, is necessary. With iodine, the reddish-brown iodide of glycogen is formed. This colour disappears on heating, but reappears on cooling. Similarly, the colour is discharged on the addition of alkalies, and reappears on slightly acidifying with hydrochloric acid. Glycogen, if free from glucose, does not reduce cupric oxide. It is precipitated by basic lead acetate.

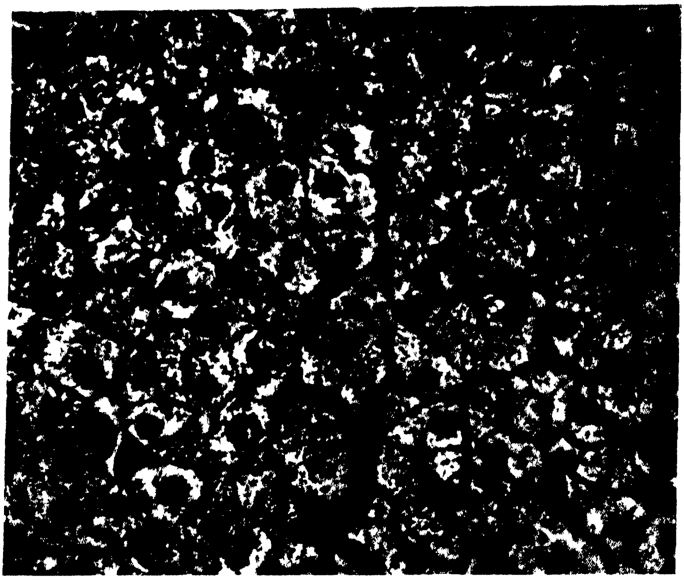

Fig. 102. Section of human liver to show liver-cells which had been loaded with glycogen which has been dissolved out, leaving clear spaces. From biopsy-material, fixed immediately after removal. × 420.

Microscopically, glycogen appears in the cell in the form of small granules or droplets. In ordinary sections which have been treated with water, these are dissolved out, leaving vacuole-like spaces (Fig. 102). In sections fixed with alcohol, the characteristic golden-brown reaction is obtained with iodine, and more permanent preparations may be made by staining with lithium carmine (Best's stain). In blood-films it may, when present in the polymorphonuclear leucocytes, be demonstrated by staining with iodine.

AMYLOID (or WAXY) DEGENERATION [1]

This condition was first described by Rokitansky in 1840 as **Lardaceous disease** because of the resemblance of the affected organs to bacon. In 1845, Dr. Budd, of Bristol, called it **waxy disease** because of the naked-eye appearance of the organs. The material, when analysed, was found to be **albuminous** in nature. In 1854, Virchow studied the condition and came to the conclusion that the substance found in the tissues was of the nature of animal cellulose because of its reaction to iodine and sulphuric acid, and he gave to it the name of **Amyloid.** This name is now generally applied in spite of the fact that later analyses have shown it to be **protein** and *not* cellulose in nature.

The condition of **amyloid degeneration** is characterised by a peculiar change **in the finer connective-tissue elements of the parts affected, whereby these swell,** become homogeneous and translucent and give certain specific chemical and staining reactions.

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[1] Greek, ἄ-μυλος, *a-mulos* or *amylos*, *not* ground at the mill, *i.e.*, prepared more carefully than by common grinding, hence the finest meal, and ἄμυλον, *amylŏn*, starch.

Ætiology. Amyloid deposition, although previously of frequent occurrence in this country, is now comparatively rarely seen. When now found, it has usually been preceded by **chronic tuberculosis.** It may, however, also follow **long-standing suppuration,** especially in bone. It occurs also in **syphilis.** It has been noted occasionally in a number of other conditions such as malignant disease, chronic rheumatism, chronic valvular disease of the heart, leukæmia, lymphadenoma, chronic malaria and chronic dysentery.

Experimentally, it has been produced by injecting animals repeatedly with staphylococci. Turpentine-injections have also caused it. Mice are very susceptible and have developed amyloid change after injections of "nutrose" (sodium caseinate); even feeding them with cheese has given rise to it (Smetana, 1925). In these experiments on mice injected daily with nutrose, amyloid was found as early as at seventeen days after the first injection. Amyloid change has been produced in rabbits by injections of sodium caseinate. It has also been found in horses injected repeatedly with diphtheria-toxin for the production of antitoxin. All these procedures have this in common that they cause an absolute increase of globulin in the blood, and Eklund and Reimann (1936) have shown this experimentally in rabbits. Chronic hyperglobulinæmia would thus appear to be an important factor in the production of amyloid. As the excess protein becomes deposited in the tissues from the blood, amyloid is formed and the hyperglobulinæmia diminishes.

Chemistry.[1] The published results of chemical analyses are somewhat conflicting. Krawkow in 1897 stated that "amyloid" consisted of a combination of protein with chondroitin-sulphuric acid. Hansen (1908) and later Eppinger (1921) found no sulphur, phosphorus or carbohydrate, but a mixture of amino-acids. Though no sulphur was found in pure amyloid, an increase in sulphur, as sulphate, occurred in the affected organs, and, in spite of the fact that there seems to be doubt as to the presence of sulphur in the amyloid itself, observers have reported an excretion of chondroitin-sulphuric acid in the urine in amyloid kidney, or its presence in the blood in cases of amyloid. Neuberg (1904) and others found the protein constituent of amyloid to resemble similar substances present in the walls of the normal aorta; this substance had a high content of diamino-acid nitrogen. The findings varied considerably in specimens of amyloid from different organs. Amyloid appears to have some resemblance to the nucleo-proteins. It is slowly digested by pepsin and more rapidly by trypsin; it is readily destroyed by autolytic enzymes. It is soluble in strong alkalies, but is little affected by acids. Physically, it is an emulsion-colloid in the gel state.

Deposition. Amyloid is deposited **in the intercellular material of the tissues,** and *not* in the cytoplasm of cells. It would appear to soak into the formed elements from the blood or lymph and accumulate in them as the result of damage to the tissues by various deleterious substances. Smetana (1927) brought forward some evidence to indicate that amyloid may be formed and deposited by cells of the reticulo-endothelial system.

Staining Reactions. It may be stained a deep brown with **Iodine.** This test is of use for the naked-eye demonstration of amyloid, though occasionally individual examples fail to give it. For microscopical sections, **methyl violet** is specific, giving a bright pink colour to the amyloid, while the unaffected structures stain blue. *Cresyl violet and methyl green give a similar metachromatic staining.* **Congo red** also is useful, the amyloid showing up as orange-red against a yellowish background. This dye will also stain and be absorbed by amyloid intravitally and hence may be used clinically to test for the presence of the disease. The stain is introduced intravenously and a sample of blood taken after an hour. Normally, only about 30 per cent. of the stain disappears, but in amyloidosis 60 to 100 per cent. may fail to show, owing to its having been taken up by the amyloid. This intravital staining may persist for days and still show in the amyloid material at autopsy.

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[1] For a detailed account of the chemistry of amyloid, see "Chemical Pathology," by H. Gideon Wells, 5th ed., 1925. Saunders Co., Philadelphia and London, p. 469.

Organs most Frequently Affected. The organs most usually affected by amyloid disease are, in order of relative frequency, the kidney, spleen, and liver : the mucous membrane of the small intestine, and the lymph-nodes ; and, less frequently, the change is found in the stomach, large intestine, suprarenals, pancreas, bone-marrow and thyroid. It supervenes only rarely in the lungs, and is said not to occur in the central nervous system.

It is thus found especially in the organs concerned with excretion, hæmolysis, and the destruction of toxic substances ; and it is usually present in a group of several of these organs at the same time, for example in the kidney, spleen, liver, and perhaps intestine. It may, in certain instances, be found in one organ alone, for example in the kidney, but this is rare.

Changes produced in the Organs by Amyloid Disease. The naked-eye appearances produced by the disease vary considerably with its duration, and according to the organ in which it occurs. If the condition is advanced, the affected organ, *e.g.*, the **liver,** is usually enlarged—sometimes to a considerable degree. The tissue becomes firmer, denser, heavier, and more elastic, somewhat resembling india-rubber in consistence. On cutting across an amyloid liver or spleen, the edges and corners of the divided organ remain sharp and distinct (Fig. 103, p. 211), and do not collapse or become rounded. The cut surface is usually smooth, dry, and glossy in appearance, the amyloid material, which may be present in greatly varying amount, being homogeneous, dark and translucent or wax-like, and usually showing the typical mahogany-brown reaction with iodine. With this reagent the naked-eye distribution of the change is usually rendered more evident (Fig. 103) ; but, in certain cases, for some as yet unknown reason, iodine may altogether fail to demonstrate the amyloid material, even though present in great amount and easily demonstrable by methyl violet. In the case of the liver, the amyloid change is often somewhat patchy in its distribution, or it may be widespread and diffuse (Fig. 103). Before the change has become very advanced, the lobules may appear to be marked out into three concentric zones, the intermediate of these being that most affected by the amyloid disease. In the **spleen,** the change in most cases affects specially the Malpighian bodies, the condition being known as **sago-amyloid** spleen, because of the resemblance of the enlarged translucent Malpighian bodies to grains of boiled sago (Fig. 103, and Plate X, Fig. 1, opposite). The organ is usually, though not always, enlarged ; whilst in the other variety of amyloid change—**diffuse amyloid** spleen—in which especially the pulp is affected, the organ may attain a considerable size (Fig. 103, and Plate X, Fig. 2). In the **kidney,** the naked-eye changes are often complicated, and perhaps

DESCRIPTION OF PLATE X

PLATE X

Fig. 1. *Amyloid Degeneration of Spleen (Sago form).* Frozen sections stained with iodine, showing portions of two Malpighian bodies and neighbouring pulp. Upper section seen with *transmitted*, lower by *reflected light.* × 50

Fig. 2. *Amyloid Degeneration of Spleen (Diffuse form).* Frozen section stained with methyl violet. The perithelial coats of the venous sinuses and the reticulum of the pulp show amyloid degeneration. The endothelium lining the sinuses (which show chronic venous congestion) is not affected by the amyloid change. × 300

Fig. 3. *Amyloid Degeneration of Liver.* Frozen section stained with methyl violet. Longitudinal section of a vessel (a portal vein) showing implication of connective supporting tissue of the muscular coat. In the neighbouring liver-tissue, the connective tissue of the capillaries is extensively affected. × 70

Fig. 4. *Amyloid Degeneration of Kidney.* Frozen section stained with methyl violet, to show amyloid change in capillaries and afferent arteriole of glomerulus. The intertubular capillaries also show slight amyloid change. × 70

Fig. 5. *Similar Preparation.* Transverse section of medulla showing amyloid change in the straight vessels. In the large collecting tubule is seen a colloid (sometimes erroneously called an "amyloid" or "waxy") cast, which gives *no* reaction for amyloid material. × 300

Fig. 6. *Hyaline Degeneration in Vessels of Spleen.* Paraffin-section stained with hæmatin and van Gieson's picro-fuchsin, showing hyaline swelling of walls of arterioles of Malpighian bodies. The hyaline material is stained canary yellow. × 300

PLATE X, p 210

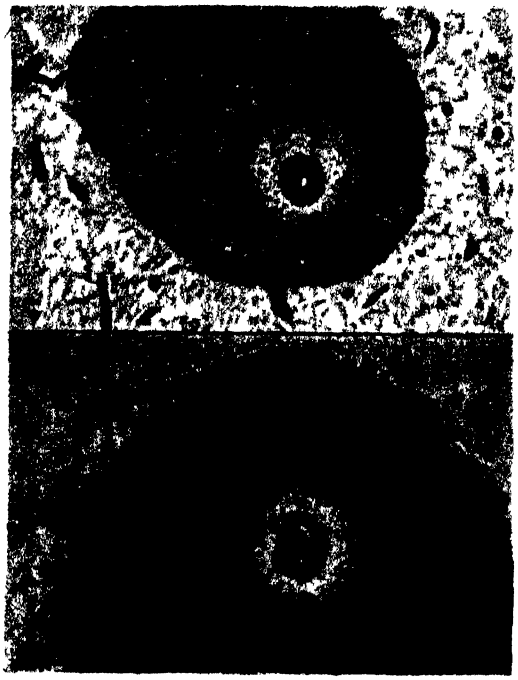
Fig 1. × 50

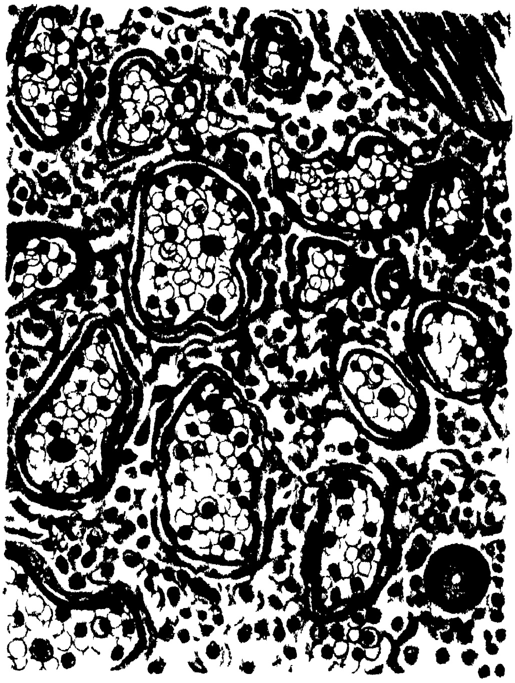
Fig 2 × 300

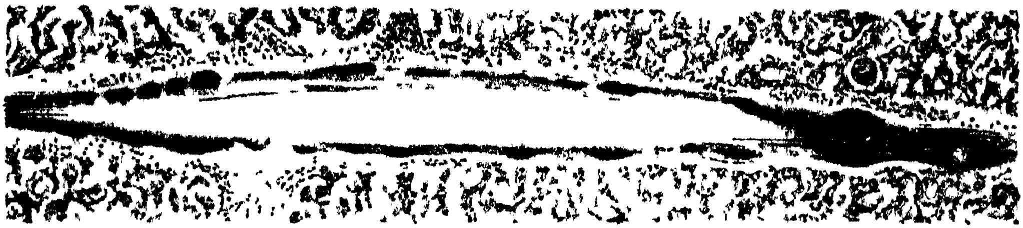
Fig 3. × 70

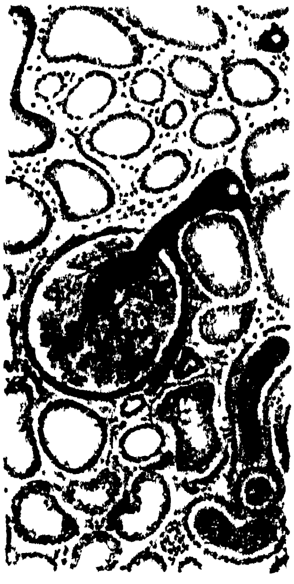
Fig 4 × 70

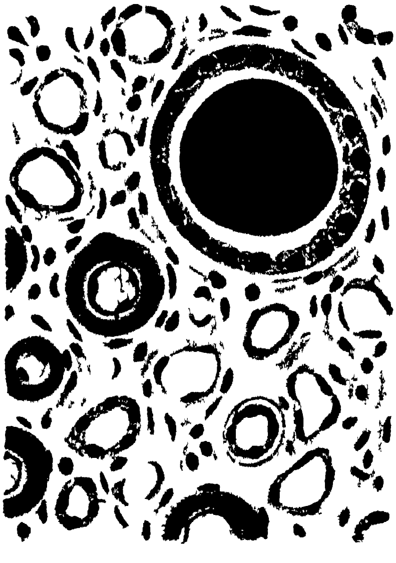
Fig 5. × 300

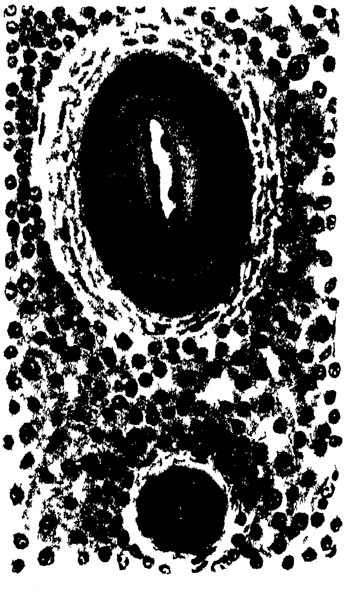
Fig 6 × 300

masked, by the presence of other associated pathological conditions which may either have preceded, accompanied or followed, the amyloid disease itself. The commonest of these associated conditions are fatty degeneration and various inflammatory changes, especially chronic nephritis. Thus, the appearances of an amyloid kidney vary indefinitely. It may be enlarged, or, if associated with chronic granular contraction of the organ, be much diminished in size. Its consistency also varies greatly. It may be firm and hard, but in some cases it is unduly soft. In more or less uncomplicated amyloid disease of the kidney—a condition rarely seen, however—there may be very slight naked-eye alteration in the organ, or it may exhibit a characteristic pale, whitish, translucent appearance in the swollen cortex and in the pyramids. Perhaps the most characteristic appearance is that seen when the disease is associated with fatty degeneration and catarrhal changes. The organ is increased in size, dull yellowish or yellowish-white in colour, with mottled opaque white or yellowish-white fatty patches, found microscopically to be catarrhal in nature, intermingled with the more translucent amyloid areas. With iodine, the lines of the interlobular arteries and glomeruli of the cortex and the straight vessels of the medulla are stained dark brown.

Sago-amyloid type. Diffuse amyloid type.

Fig. 103. Amyloid degeneration of liver and spleen. The lower parts of each section have been treated with iodine.

In the **intestine**, the mucous membrane usually undergoes catarrhal and atrophic changes ; and with iodine the amyloid vessels of the mucous and submucous coats can be demonstrated as minute dark brown specks or lines. In the **stomach**, amyloid degeneration is comparatively rare (p. 728).

Microscopical Distribution. The change attacks first the middle coats of the ultimate arterioles of the affected organ, the delicate connective tissue between the muscular fibres becoming swollen and homogeneous, and exhibiting the typical staining reactions (Plate X, facing p. 210, Fig. 3). It then spreads backwards along the larger arterioles to the smaller arteries, and forwards along the perithelial connective tissue of the capillaries to the middle coats of the small veins. It may spread to the connective-tissue framework of the affected organ, and to basement-membranes if these be present; but it should be noted that the change never affects the endothelial cells lining the vessels, the connective-tissue cells, or the glandular epithelium. In other words, the condition does *not* affect the **cytoplasm of cells**, but only the **formed collagenous elements** of the organ.

Course and Results of the Disease. Amyloid degeneration occurs in certain chronic infective diseases of protracted duration, where there is long-continued action of the resulting toxic substances upon the tissues. This is usually a question of many months. or even years, and it is probable that, in man, the condition has not been produced in less than three months. It is a progressive disease; and it is doubtful whether amyloid material, when once formed, can be re-absorbed on the removal of the cause of the condition, for example, by the excision or amputation of a chronic tuberculous joint. It is difficult to obtain any direct evidence bearing upon the point, but such re-absorption is probably possible only in cases where the disease is in its earlier stages. In experimental animals, fragments of amyloid have been seen enclosed in giant-cells, and it is thus probable that some degree of re-absorption can occur, but only if the condition is not too far advanced.

The results of the disease upon the organs may be considered under three main heads, viz. (1) the effects upon the vessels; (2) the effects upon the parenchymatous cells; and (3) the increased liability of amyloid organs to undergo irritative, inflammatory and degenerative changes, more especially fatty degeneration. To the last of these, reference has already been made, especially in the case of the kidney, in which organ there is also a greatly increased liability to various forms of nephritis—a fact which has led to the erroneous statement that "Bright's disease may sometimes lead to amyloid degeneration of the kidney," for which there appears to be no foundation in fact.

Effects on the Vessels. As stated above, the change is usually seen first in the connective tissue supporting the muscular fibres of the middle coat, especially in some of the smaller arteries (Plate X, facing p. 210, Fig. 3). Because of the great swelling of the connective-tissue fibrils in this situation, the muscle-fibres become compressed and atrophied, and may ultimately be completely destroyed, the controlling influence of the arterioles upon the circulation through the organ thus being to a great extent diminished, or even lost. The walls of the capillaries and veins also suffer. The lumen of the vessels, though often considerably narrowed by the swelling of the walls, is very seldom actually obliterated—a fact which can be demonstrated by injecting the arteries of an amyloid organ with, say, carmine, the injection passing with ease into even the smallest vessels. The special selective capacity of the wall—if such exists, as in all probability it does—must, however, be considerably affected; and this, together with the loss of the normal powers of contraction and relaxation of the muscular coat of the arteries, especially the arterioles, tends to cause an increased amount of transudation, a fact which may, in part at all events, help to explain the increased excretion of watery urine and the diarrhœa in cases where the kidney and intestine are affected by the disease.

Effects on the Parenchymatous Cells. Another point of importance is the compression and consequent atrophy of the special cells of the affected organ, produced by the great swelling of the formed connective-tissue elements, whether in the vessel-walls or in the supporting framework of the tissue. Thus, although the actual total size of the organ, *e.g.*, the liver, spleen, or kidney, may be increased, there may in reality be an advanced degree of compression-atrophy of its functioning or parenchymatous cells.

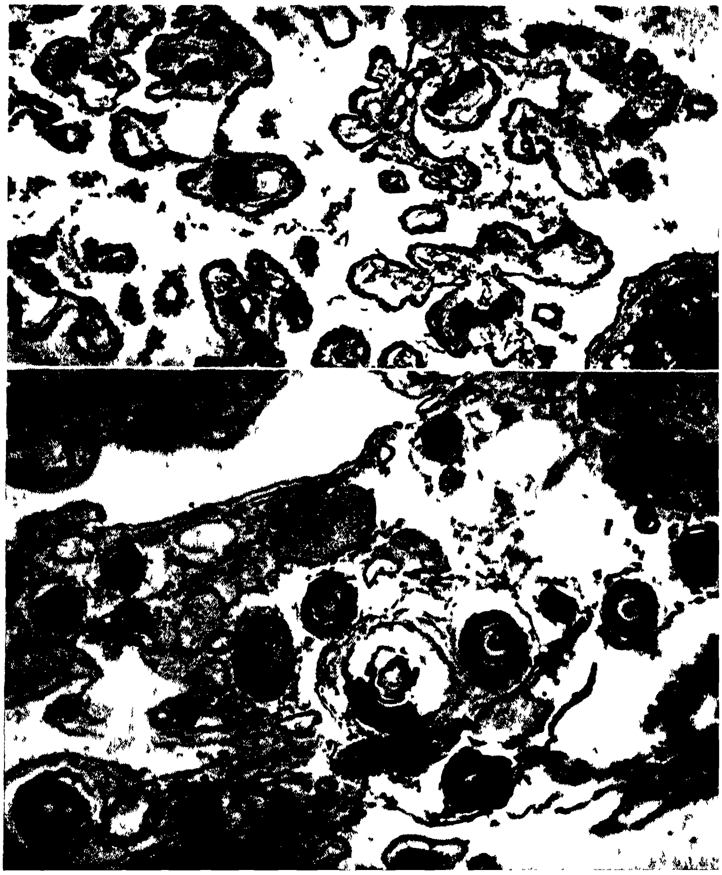

FIG. 104. "Corpora amylacea" or "corpora arenacea" in the choroid plexus. In the upper section are shown several choroidal villi in which dark patches of calcification can be seen, without, as yet, any concentric arrangement. In the lower section are a number of concentrically laminated bodies, dark-stained owing to calcification; these are the fully formed "corpora arenacea." (*Cf.* Fig. 586 on p. 971 and Figs. 712 to 714 on pp. 1123–4.) Hæmatoxylin and van Gieson's stain. × 80.

NOTE. The following conditions, which, from the somewhat misleading names applied to them, or from a superficial resemblance to true amyloid degeneration, have sometimes been confused with that disorder, should be carefully distinguished from it:—

1. **Corpora amylacea** and **corpora arenacea.** In certain positions, for example in the kidney, prostate, lungs, and, most frequently of all, in the central nervous system, small spherical or ovoid bodies are often seen, which, upon microscopical examination, are found to have an irregularly concentric laminated appearance, some-

what similar to the structure of a grain of starch—hence the name "corpora amylacea" previously applied to them.[1] These bodies have, however, *no* connection with the process of waxy or amyloid disease proper, though they may give a brownish colour-reaction with iodine. They occur also in certain tumours, and in old blood-clots and inflammatory exudates. In the case of certain tissues (*e.g.*, those of the central nervous system) which have been preserved for some time in spirit, an appearance somewhat resembling these bodies may be produced artificially. These bodies, in common with other areas of degenerated tissue, readily undergo secondary calcification, and are then more correctly termed corpora arenacea.

2. "**Amyloid tumours,**" *e.g.*, of conjunctiva. These may be inflammatory in origin or not, and appear to have no relation whatever to true amyloid degeneration.

3. **So-called "waxy" or "amyloid" casts in kidney-tubules.** These are really colloid in nature, and are due to degeneration of the tubular epithelium (Plate X, Fig. 5).

4. **Zenker's degeneration of muscle** (p. 248), really a necrotic or post-necrotic change.

5. "**Localised amyloid degeneration,**" so-called, occurring around chronic abscesses and in the walls of old sinuses, etc. It is extremely doubtful whether this condition is in any way related to true amyloid disease.

HYALINE DEGENERATION

The term "Hyaline Degeneration" is used merely to describe the physical appearances of the tissues and is not in any way an indication of chemical composition. As a consequence, therefore, many diverse conditions have had the term applied to them, *e.g.*, certain changes in degenerating epithelial cells ("cancer-bodies," various cell-inclusions, etc.), fusion of the blood-platelets in capillaries ("hyaline thrombi"), hyaline casts in the tubules of the kidney, corpora amylacea, etc. We propose to restrict—perhaps rather arbitrarily—the use of the term to those peculiar changes found in the connective-tissue elements in the walls of the smaller arteries and of the capillaries, and in some other positions, produced under the influence of certain toxic substances, whereby the delicate connective-tissue fibrils tend to swell and become more homogeneous, refractile and transparent in appearance, and more resistant to the action of digestion and of chemical agents.

The change is toxic in origin and is found especially in some of the more acute infective conditions, *e.g.*, diphtheria and scarlet fever. It may, however, occur also in certain forms of chronic renal disease, and in some other long-standing toxæmic conditions.

Nature and Distribution of the Change. The change is essentially degenerative in the delicate supporting connective-tissue fibrils, especially of the inner, and to a less extent of the outer, coat of the smaller arterioles, but it may occur, though more rarely, in the middle coat, and it may also affect the perithelium of capillaries. It is found especially in the spleen and kidney, in the brain, spinal cord, pia-mater, and less commonly in lymph-nodes and other tissues. A well-marked degree of the change is often found in the ovary as age advances, and the degenerated hyaline remains of neighbouring vessels may coalesce to form one type of the so-called corpora albicantia of common occurrence in that organ (Fig. 105, opposite).

In these situations, the connective-tissue fibrils in the vessel-wall tend to swell and fuse together, and so to form irregularly-distributed, clear, homogeneous, transparent, structureless masses, which may encroach upon or even obliterate the lumen of the affected vessel, and may lead to secondary changes such as thrombosis, degeneration or actual necrosis in the area of supply. The hyaline material does not appear to have any very definite chemical composition, though it is said to be allied to elastin and keratin. Its staining-reactions are somewhat variable, but it has usually a distinct affinity for some of the acid dyes, taking on a red colour with eosin or with acid fuchsin, especially when the hyaline material is of recent formation. Two of the most convenient stains for the demonstration of the condition are picro-carmine and picro-fuchsin (van Gieson's stain). With the former of these, in the earlier stages it takes on a pinkish tinge, whilst later it stains yellow with the picric-acid part of the dye. With van Gieson's stain, recent hyaline material usually shows a bright red colour, but later it tends to stain a characteristic orange-red, orange or ultimately even a bright canary-yellow colour (Plate X, opposite p. 210, Fig. 6). The change, unlike amyloid degeneration, is very irregular and patchy in its distribution. It does not give the characteristic "amyloid" reactions with iodine and methyl violet.

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[1] Corpora arenacea: *see also* pp. 321–3: Fig. 104, p. 213; Figs. 671 and 674, pp. 1091–3; and Figs. 712–14, pp. 1123–4.

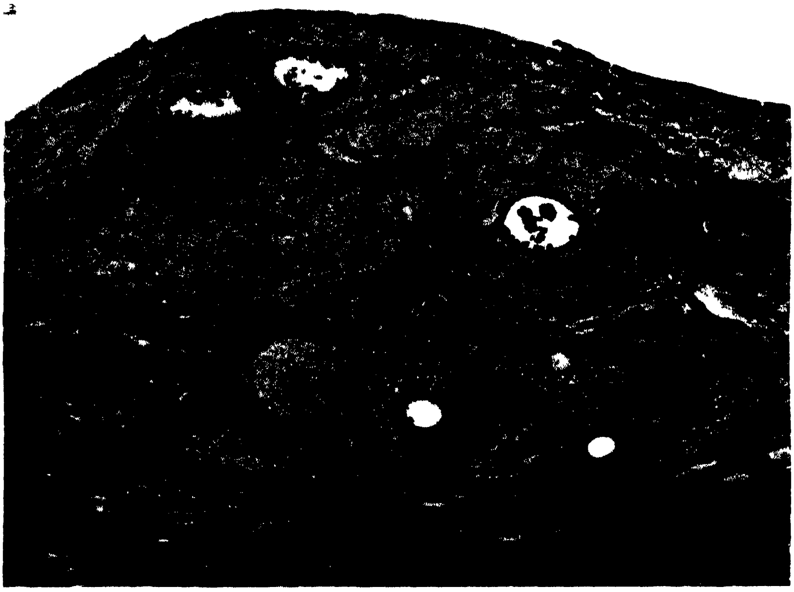

FIG. 105. Hyaline degeneration. Small arteries of ovary, undergoing degeneration, with tendency to coalesce and form one type of corpus albicans. Hæmatoxylin and van Gieson's stain. × 120.

The condition of hyaline degeneration leads to no special naked-eye changes in the organs, microscopical examination being necessary for its detection. It may be followed by calcification, for example in the arterioles of the kidney and spleen.

GOUTY DEGENERATION AND INFILTRATION

Into the general subject of gout and the chemical details of the metabolism of the nucleo-proteins, nucleins and purines, and their end-product, uric acid, we do not propose to enter. The subject is extensive and does not come within the scope of the present volume, and we refer those interested in it to such special works as Harrison's "Chemical Methods in Clinical Medicine" and Wells's "Chemical Pathology."[1]

It will suffice to say that uric acid is derived largely from the breaking-down of the nucleo-proteins both of the food and of the body-tissues, especially from the destruction of the nuclei of normoblasts (p. 592), being readily produced from the purine-bases contained in these substances, under the influence of specific enzymes or ferments. Uric acid is eliminated as such in the urine only to a small degree, the larger proportion being oxidised by enzymes in the liver, kidney, muscles, etc., and converted into urea, in which form it is excreted by the kidneys.

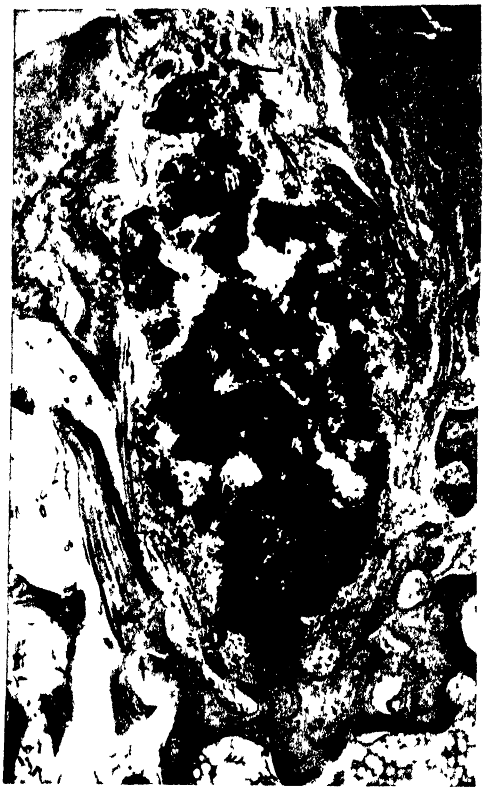

FIG. 106. Gouty deposit in bone. Hæmatoxylin and eosin. × 20.

The amount of uric acid in the urine and in the blood therefore varies in any given case, and is dependent upon many factors. The amount of uric acid and urate crystals deposited in the urine, depending upon such factors as temperature, reaction, concentration, amount of neutral phosphates present, etc., is probably a matter of comparatively minor importance; and Wells states that there is "no good evidence which makes it probable that uric acid is responsible for any pathological conditions whatever, except uric-acid calculi, 'uric-acid infarcts' in the kidneys, and certain manifestations of gout. Uric acid is possessed of but a very slight degree of toxicity, and the body is able to get rid of it in such large measure that an actual intoxication with uric acid probably never occurs."

In patients subject to gout, especially during the periods between the acute exacerbations, there appears to be no special abnormality in the amount of uric acid excreted in the urine, although the amount present in the blood is said frequently to be greater than it is in health. Such increase, however, is often slight or even absent. It rarely exceeds values of 10 mgr. per 100 c.cm., and, indeed, larger increases are often found in many patients suffering from chronic nephritis. Moreover, these two conditions frequently co-exist. That this increase in the amount of uric acid in the blood in gout is not due to a diminished capacity on the part of the kidneys to excrete uric acid is said to be proved by the experimental subcutaneous injection of uric acid into gouty subjects, the excretion in the urine occurring as rapidly and readily as in normal persons. Just before an acute exacerbation, the amount of uric acid excreted in the urine is usually diminished; whilst during and immediately after the acute attack the amount may be considerably increased.

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[1] G. A. Harrison's "Chemical Methods in Clinical Medicine," 2nd Ed., J. & A. Churchill, London, 1937, Chapter XIX, p. 385. Wells' "Chemical Pathology," Saunders Co., Philadelphia and London, 1925, Chapter XXV, p. 716.

Whatever the relationship between uric-acid metabolism and gout may be —and from recent work on the subject it appears more than likely that its variations are to be regarded rather as the *result* than as the cause of the disease —it is possible to describe briefly the lesions characterised by the deposit of uric acid, chiefly in the form of mono-sodium or acid sodium urate ($NaH\bar{U}$), in certain situations.[1] This acid salt of uric acid is deposited in the form of granules or of acicular crystals (Figs. 106–7) ; more especially in the articular cartilages and ligaments of joints : in bone and in tendons and tendon-sheaths : in the cartilages of the ear and eyelids : in the fibrous tissue of the heart-valves : in the interstitial tissue of the kidney : and in the subcutaneous fibrous tissue, especially in the neighbourhood of joints. In the last of these situations, considerable deposits are sometimes found, forming the so-called chalk-stones or "tophi," which may become exposed by the ulceration and destruction of the skin over them.

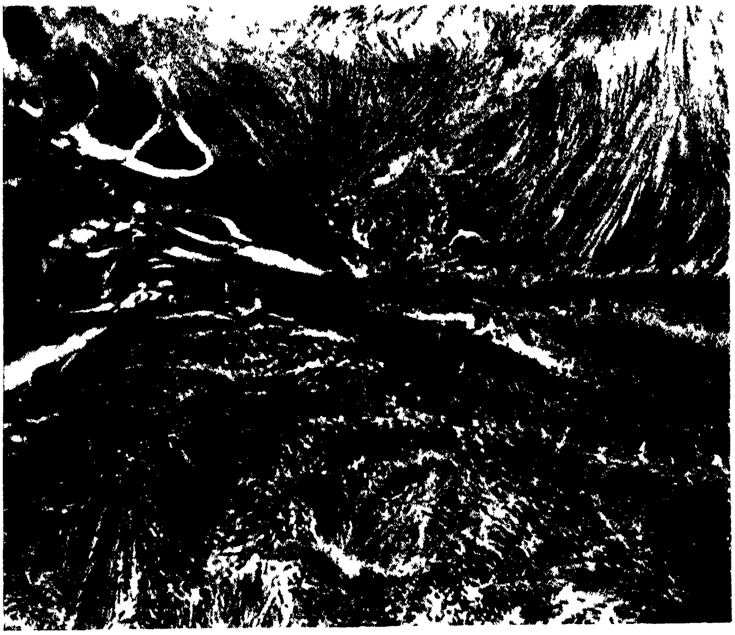

FIG. 107. Gouty deposit in subcutaneous tissue, showing the acicular crystals of acid sodium urate. Note the surrounding cellular reaction, and formation of "foreign-body giant-cells." Hæmatoxylin and eosin. × 500.

The condition tends first to involve the structures in and around some of the smaller joints, *e.g.*, of the foot or hand, more especially the metatarso-phalangeal joint of the great toe. The larger joints, *e.g.*, the knee-

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[1] The following analysis of such deposits, by Ebstein and Sprague, is given by Wells (*loc. cit.*, p. 523):—

Uric acid	59·70	Potassium oxide	2·95
Tissue organic matter . . .	27·88	Calcium oxide	0·17
Sodium oxide	9·30	MgO, Fe, P_2O_5, S	traces

"After a time, however, calcium salts may be deposited, and Dunin has observed deposits resembling gouty tophi that were merely calcium salts."

joints, may become involved later. The earliest changes occur in the more superficial layers of the articular cartilages, especially in the cartilage-cells, which proliferate, become swollen, and undergo degenerative changes (p. 1234). It is in and immediately around these degenerating cells that the granules and acicular crystals of acid sodium urate are deposited, whilst later they are found also in the intervening matrix. The cartilage, especially towards the surface, becomes opaque white, and has the appearance of having been " smeared with plaster of Paris," or " streaked with white paint." Later, it may become necrotic, split up and undergo ulceration. Accompanying these phenomena, there is usually a varying amount of acute, and, later, of more chronic, inflammatory change in the fibrous structures of the joints and the other surrounding parts.

Ætiology. The cause of gout is still unknown. It has long been regarded as a disease due to some " error in metabolism," but the cause and exact nature of the error have still to be discovered. An almost identical series of changes is *found in the joints in the so-called " lead-gout " occurring in chronic lead-poisoning, which also tends to produce changes in the kidney similar to those seen in ordinary gout.*

PATHOLOGICAL PIGMENTATION

The group of conditions commonly known as the " Pathological Pigmentations " includes the results of many diverse processes, some of which are obscure in their nature and ætiology. It is convenient to classify them under the following headings :—

I. Abnormalities in the amount or distribution of the normal animal pigments, and of pigments closely allied to these.

II. The presence of hæmatogenous pigment, *i.e.*, pigment derived from the hæmoglobin of the red blood-corpuscles ; and along with this we may also consider the so-called hepatogenous pigmentation due to the deposit of bile-pigment, which is derived from the destruction of hæmoglobin by the reticulo-endothelial cells.

III. The presence of extraneous pigmentary substances, *i.e.*, introduced into the tissues from without.

IV. Discolorations of the skin due to parasites. These do not call for further notice here, and descriptions of them will be found in text-books on Dermatology.

V. Discolorations of the organs and tissues due to post-mortem decomposition (p. 236), and the analogous changes in gangrene (p. 251)

I. ABNORMALITIES IN THE AMOUNT OR DISTRIBUTION OF THE NORMAL ANIMAL PIGMENTS AND THE PRESENCE OF PIGMENTS ALLIED TO THEM —ENDOGENOUS PIGMENTATION

The origin and chemistry of the normal pigments of the body are still subjects about which little is known. Some of these pigments, *e.g.*, those found in the skin, hair, uveal tract of the eye, and certain other localities, appear to be allied to the albumins ; whilst those found in the corpus luteum, testes, suprarenals, nerve-cells, and in adipose tissue, are of the nature of coloured fats or fatty compounds, and are known as the lipochromes.

To the pigments belonging to the former of these groups the general name **melanin** is given. These melanins vary considerably in their composition in the different tissues. They all contain nitrogen, hydrogen, and carbon (usually in the approximate relative proportions 1 : 5 : 5). Many of them have also a comparatively high sulphur-content, although this element is said to be absent in the case of the melanin found in the choroid coat of the eye. In melanotic tumours (p. 323), the characteristic pigment is closely allied to, or identical with, normal melanin, and may contain a large amount of sulphur—sometimes as much as 10 per cent. Some, though by no means all, of the melanins, have been described as containing iron, usually only in very small amount, but both iron and sulphur are stated by Bloch (1929) to be impurities derived from the tissues from which melanin is extracted.

The melanins are the product of the metabolic activity of special cells, *i.e.*, they are built up by the living protoplasm, and are not merely the disintegration-products of hæmoglobin or its derivatives. In all likelihood they are derived from the complex protein-molecule (probably from its aromatic chromogen molecular groups), possibly under the influence of specific ferments or enzymes.

The melanins are insoluble in most of the ordinary solvents, *e.g*, water, alcohol, chloroform, benzol and ether. They are soluble in dilute alkalies, and in concentrated sulphuric acid. They are practically unaffected by even boiling strong hydrochloric acid, but are readily decolorised by strong alkalies, by hydrogen peroxide, chlorine and other bleaching reagents, and by the action of sunlight. The majority of the melanins yield *indole and scatole when fused with caustic potash. Fatty acids, and an acid belonging* probably to the aromatic series which gives a blue colour with ferric chloride, have also been isolated from the products of fusion with caustic alkali. The chemical evidence seems to indicate tryptophane, tyrosine, and adrenaline as the most probable sources of the melanins. Tryptophane, like all indole-derivatives, is a labile substance which readily undergoes conversion into pigments having properties similar to those of the melanins. Further, the enzyme tyrosinase, by a process of oxidation, converts tyrosine into a dark-brown pigment closely resembling the melanins. Adrenaline shows a similar tendency to undergo oxidation to dark-brown pigments.

"**DOPA-Reaction.**" B. Bloch (1917) was the first to show that certain cells of the skin could oxidise 3-4 : **D**i-hydr**O**xy-**P**henyl**A**lanine to melanin. This substance is an intermediate product in the formation of melanin from tyrosine by the action of the ferment tyrosinase, and is related chemically to adrenaline. It is called "**DOPA**" for short, and the product of the "**DOPA-reaction**" is "**DOPA-melanin.**" (For a further note on the "DOPA-reaction," *see* p. 323.)

The cells which give this reaction do so by the action of a ferment which they possess. Cells capable of giving it are the epithelial cells of the basal layer of the skin, *i.e.*, cells of epidermic origin, certain pigmented cells of the meninges, some branching cells of mesodermic origin in the corium of the skin, the cells of the ciliary body and of the choroid coat of the eye, and leucocytes and myelocytes of the granular series.

These pigments are usually intracellular, and are commonly in the form of minute yellowish-brown, brown, or brownish-black granules, which may be scattered throughout the cytoplasm, or in some cases are so densely packed as entirely to obscure the cell-structure.

Pigment may be found in cells which have actually produced it, or in those which may have merely ingested it. Cells which *produce* pigment are known as "chromatoblasts" ("melanoblasts" in the case of melanin); those which have merely *ingested* it, *e.g.*, ordinary phagocytes, are termed "melanophages" (by some writers called "chromatophores" or "melanophores," *i.e.*, pigment carriers—pp. 323–4). Melanoblasts are usually dopa-positive, melanophages are dopa-negative.

Congenital deficiency, or even the entire absence of the normal pigments, is seen in the condition known as **albinism.** In **vitiligo** or **leucoderma,** the cutaneous pigment becomes irregular in its distribution, some patches becoming paler than normal owing to the deficiency, whilst surrounding areas may show an increase of pigment. Again, after the repair of wounds and ulcers, especially if these are of any extent, the scar-tissue is frequently deficient in pigment, and may therefore be whiter than the surrounding skin, and this contrast may, indeed, especially if there has been any chronic irritation and delay in the healing process, be accentuated by an actual increase of pigment in the skin immediately around the scar. Localised deficiency of skin-pigment may also be due to trophic and nervous causes—for example, the white patches in leprosy due to implication of the cutaneous nerves (pp. 79 and 1187).

Increase of pigment is, however, a condition encountered more frequently than deficiency. Such increase may be physiological, *e.g.*, in the case of the mammary areola during pregnancy. "Sunburn" and "freckles" may also be regarded as a physiological reaction to the stimulation of light, the increase of surface pigment serving to protect the deeper structures against the harmful action of the too powerful actinic and other rays, in the same way as does the pigmented skin of the negro. Localised pigmentation may also result from irritation of the skin, caused, for example, by a blister, parasites, certain skin-diseases, etc.

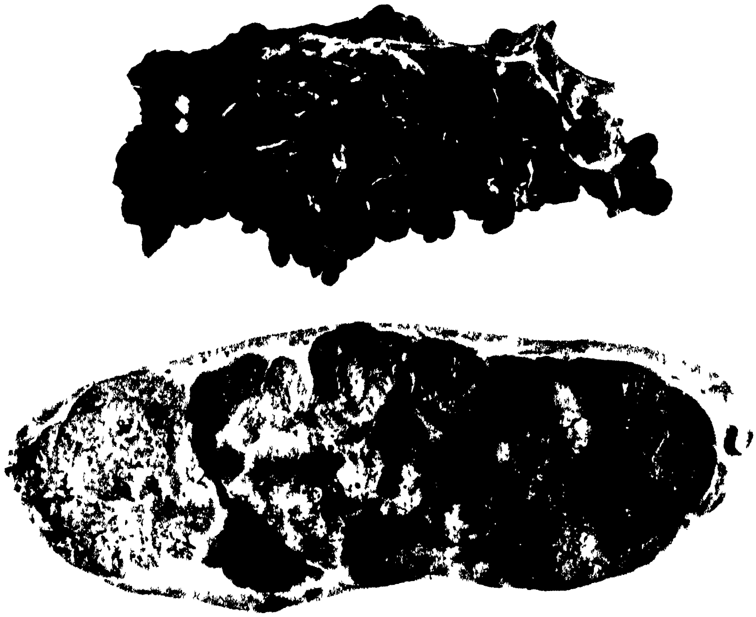

FIG. 108. Malignant melanoma, showing pigmentation. In the lower specimen, a secondary nodule in the subcutaneous tissue, the distribution of the pigment is very irregular.

Pigmentation is often, however, an accompaniment or a result of certain retrogressive or degenerative and atrophic processes, occurring sometimes as a senile change, sometimes as the result of disease.

Above the age of forty or forty-five, the fine granules of pigment found in the cytoplasm of heart-muscle fibres towards the poles of the nucleus tend naturally to increase both in size and number as age advances, the fibres at the same time becoming smaller (p. 464). This condition may in certain cases be exaggerated in degree, or it may occur at an abnormally early age, for example in cachectic or wasting diseases such as cancer or chronic phthisis, and is then known as **brown atrophy** of the heart (Plate XI, Fig. 4, p. 222). This pigment found in the myocardial fibres in brown atrophy is a **lipochrome** (pigmented fat). Such senile pigmentary changes may be found, not only in heart-muscle, but also in the kidneys, liver, suprarenals, muscular coat of the intestine, pia-arachnoid, and nerve-cells. The ingestion of certain vegetable pigments, such as "carotene" (or "carotine"), may cause an increase of this pigmentation and also increase the yellow colour of fatty tissue.

FIG. 109. Malignant melanoma, showing accumulation of melanin in certain of the tumour-cells. × 350.

In wasting conditions, the skin-pigment is often abnormally increased in amount, especially over the flexures and in other parts where there is normally a greater amount of skin-pigment present. Abnormal increase of **cutaneous melanin-pigment** is found especially in chronic ovarian and uterine disease (the so-called "chloasma uterinum"); and in chronic diseases of certain other glandular organs, more especially of the suprarenal (or adrenal) bodies, destruction of which may lead to Addison's disease (p. 843 *et passim*), a condition which is characterised by great muscular weakness and wasting, and by brownish pigmentation of the skin, particularly where this is exposed to the action of sun-light, friction, or other form of irritation. Irregular patchy pigmentation of certain of the mucous membranes, *e.g.*, of the mouth, is also characteristic of this disease. The nature of the pigment has not yet been determined, but it is probably identical with or closely allied to the normal melanin-pigment of the skin. The increase is ascribed to the loss of the cells of the suprarenal medulla, which normally form adrenaline. The precursors of this substance are not utilised and accumulate ; they are acted on by enzymes and converted into pigment in situations where normally this is formed, *e.g.*, the skin.

Local increase of melanin-pigment is seen also in connection with certain tumour-growths, *e.g.*, in pigmented moles, or more notably still in malignant melanomas (Figs. 108–9). The cells of such tumours give a positive dopa-reaction. In these the melanin, which may be in large amount and often highly irregular in its distribution, is contained mostly within the tumour-cells. It may, however, be found in phagocytes, or free in the lymphatic spaces, and may also be present in the blood and lymph, and in pronounced cases it may even be excreted in the urine by the kidneys either as melanin or more usually as the colourless melanogen. Urine containing the latter is normal in colour when passed, but darkens slowly from the surface downwards on standing or on the addition of oxidising agents—these conditions being known respectively as **melanogenuria** and **melanuria.**

"Melanosis" of the Colon. The mucosa of the large intestine is sometimes deeply pigmented, almost black in colour, from the presence in the epithelial cells and sub-epithelial tissue of granules of black pigment, the exact nature of which is uncertain. It may be a melanin, derived probably from excessive decomposition in the intestine from chronic constipation, but it does not give the typical melanin-reactions.

Ochronosis is a rare condition of brownish pigmentation of the cartilages of the body. In some of these cases, **alkaptonuria** is also found, a condition due to defective splitting of the protein molecule with accumulation of pigmentary derivatives which appear in the urine, giving it, on standing, a dark brownish-black colour from the presence of homogentisic acid.

Reference has already been made to the presence in the tissues of certain pigmented fatty bodies or **lipochromes,** *e.g.*, the lutein found in the corpus luteum : or the pigment seen in the suprarenal cortex, or in many ganglionic cells, both normally in certain parts of the nervous system, and abnormally in some forms of degeneration of nerve-cells (Figs. 766–7–8, pp. 1194 to 1197). Lipochromes are found in some pathological conditions, *e.g.*, in xanthoma or xanthelasma, in which there are developed small yellowish tumour-nodules, especially in the skin of the eyelids : and in chloroma (pp. 319, 636 and 1231), a rare disease characterised by the development of leukæmia and of peculiar greenish-coloured lymphomatous or lymphosarcoma-like growths, more especially in connection with the bones. It may also be of interest to note here that many of the pigments produced by bacteria appear to be of the nature of lipochromes, *e.g.*, in the case of cultures of *Staphylococcus pyogenes aureus* or *citreus*.

The **chromaphil** (or so-called "**chromaffine**") **tissues**, which include the **suprarenal medulla** and many of the cells of the **sympathetic** system, have an affinity for chrome-salts and are thus demonstrable histologically by treatment with fixatives containing these salts (pp. 840–1 and 846). The reaction depends on adrenaline (epinephrine) or allied substances produced by these cells. Tumours arising from such tissues may give the same reaction (pp. 648 and 756). The **carotid body—glomus caroticum** (p. 849)—was formerly believed to belong to this chromaphil group of tissues, but the cytoplasmic granules of its cells, although they stain with chrome-salts, do *not* contain adrenaline, and this little organ is now believed to be sensory, and not endocrine, in function. For a note on the "xanthopterine" secretion-granules in the "**argentaffine cells**" of the gastro-intestinal tract, and their relationship to the production of Castle's hæmopoietic factor, see pp. 648 and 756.

DESCRIPTION OF PLATE XI

PLATE XI

Fig. 1. *Hæmatoidin-crystals,* free and contained in phagocytic cells in an organised thrombus in a vein. Stained with hæmatoxylin. × 1000

Fig. 2. *Phagocytic cells (from bone-marrow) containing blood-pigment.* Stained with methylene blue and eosin. One cell also contains an ingested red blood-corpuscle. × 1000

Fig. 3. *Addisonian Anæmia.* Section of liver treated with potassium ferrocyanide and hydrochloric acid, to demonstrate by the Prussian-blue reaction the presence of *hæmosiderin* in the liver-cells. Counterstained with safranin. × 1000

Fig. 4. *Brown Atrophy of Heart.* Longitudinal section of muscle-fibres stained with alum-carmine. The unstained yellow pigment is seen in the cytoplasm, especially towards the poles of the nuclei. × 1000

Fig. 5. *Obstructive Jaundice.* Section of liver, stained with alum-carmine, showing masses of dark-green *bile-pigment* in the liver-cells, which also contain some yellow *blood-pigment.* The nuclei seen are those of the liver-cells. × 1000

Fig. 6. *Large phagocytic cells* (probably reticulo-endothelial in origin) *containing carbon-pigment.* These cells are from a case of anthracosis, in which they were present in large numbers in the pulmonary alveoli. Stained with methylene blue and eosin. × 1000

PLATE XI, p. 222.

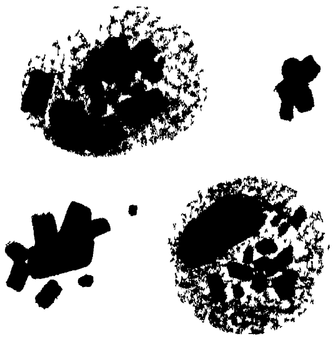

FIG. 1. × 1000

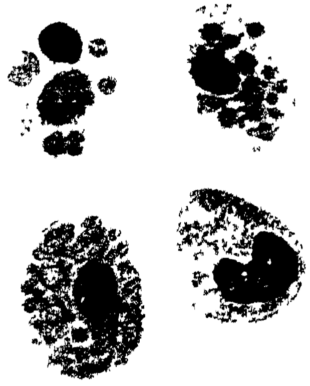

FIG. 2. × 1000

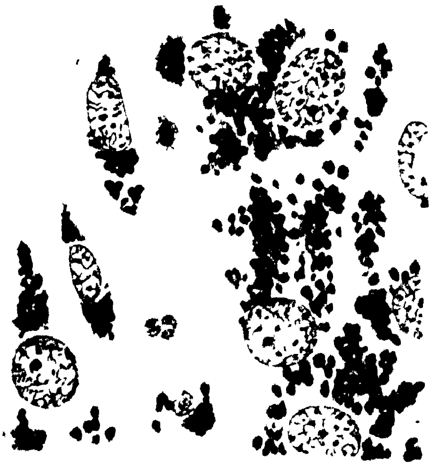

FIG. 3. × 1000

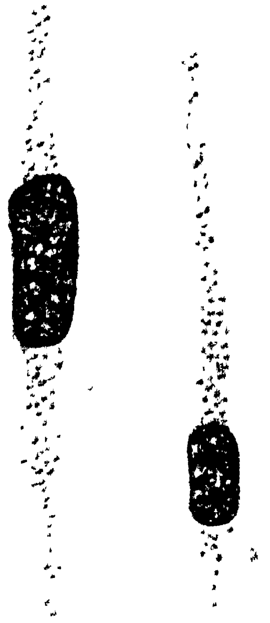

FIG. 4. × 1000

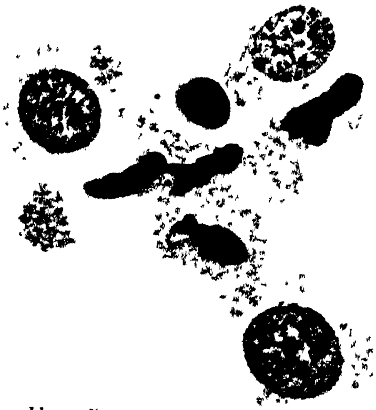

FIG. 5. × 1000

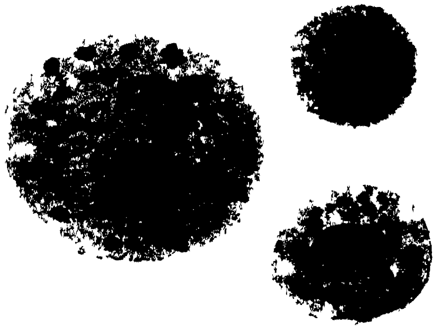

FIG. 6. × 1000

II. HÆMATOGENOUS PIGMENTATION

Under certain circumstances, pigment derived from the hæmoglobin of the red corpuscles may be found in the tissues or elsewhere. The presence of such hæmatogenous pigment may be the result of a direct attack by organisms upon the red corpuscles themselves while circulating in the vessels, *e.g.*, in malaria, the parasites in the corpuscles attacking and feeding upon the hæmoglobin, and forming yellowish-brown granules of pigment, to which reference will be made later (pp. 227–8 and 381).

Again, the erythrocytes may be damaged by bacterial and other toxins or poisons, and may break down whilst still circulating in the vessels, their contained hæmoglobin being discharged into the plasma. More commonly, however, the damaged corpuscles are, before their disintegration, taken up and digested by phagocytic cells : a process which occurs more especially in the organs normally concerned with hæmolysis, viz., the liver, spleen, bone-marrow, lymph- and hæmolymph-nodes. In diseases such as untreated Addisonian and other grave forms of anæmia, hæmoglobinuria, malaria, etc., the amount of pigment so derived may sometimes be very considerable in the cells of these and other organs and tissues (Plate XI, opposite, Figs. 2 and 3).

In some instances, such hæmatogenous pigment may be formed from the hæmoglobin of blood which has undergone thrombosis within the vessels, or which has been effused into the tissues or into some natural cavity. Or, again, the occurrence of this variety of pigment may be due to stagnation of the blood, for example, in chronic venous congestion. In the case of the lungs in this last-mentioned condition, the abundant pigment found in the large mononuclear phagocytic cells in the alveoli is due to small hæmorrhages into the air-vesicles (Figs. 69 and 70, p. 150). In the case of the liver, the pigment is found especially in the hepatic, and also in the phagocytic reticulo-endothelial or von Kupffer's, cells (Fig. 74, p. 154). It is probably evidence of increased hæmolysis, a condition favoured by the stagnation of the blood.

The Nature and Occurrence of Hæmatogenous Pigments. Hæmoglobin, the normal pigment of the red corpuscles, is a conjugated protein which can, by chemical means, be split up into a simple globulin (globin) and the non-albuminous iron-containing pigment hæmatin.

Hæmoglobin is soluble in water and plasma but can be crystallised out only with difficulty from human blood. It crystallises more readily from the blood of rats and guineapigs in the form of orange-coloured rhombic prisms or plates. It is insoluble in glycerine, which can, therefore, be used as a mounting-fluid for microscopical preparations of it. It is non-toxic and may diffuse into tissues, giving a reddish-yellow colour to them ; this is seen, *e.g.*, in the aorta and heart in cases where post-mortem autolysis is advanced. In hæmolysis it may be present in the blood-plasma, colouring it, and if enough is present in the plasma it may appear unchanged in the urine, *e.g.*, in paroxysmal hæmoglobinuria (*see* pp. 227 and 659–661). Normally it is contained within the red corpuscles.

Even in health, the red corpuscles are comparatively short-lived, and, as they become effete, are constantly being destroyed by the cells of the reticulo-endothelial system, especially in the liver, spleen, bone-marrow, and hæmolymph-nodes. The albuminous globin-radicle is digested and absorbed, whilst the pigment, hæmatin, is split up into two fractions, an iron-free substance called hæmatoidin, excreted principally by the liver as bilirubin, with which it is apparently identical in chemical composition : and secondly, an iron-containing moiety called hæmosiderin (or " blood-iron "), which is stored in certain of the tissues, especially the liver, spleen, and bone-marrow, to be built up again into hæmoglobin as required.

An exaggeration of these normal hæmolytic processes may occur in disease, usually under the influence of bacterial or other toxins and poisonous substances. In some conditions, this increased hæmolysis may be very pronounced, for example, in the anæmias, more especially in untreated Addisonian anæmia. Evidence of this exaggerated destruction of red corpuscles is to be found in the excessive formation and storage of hæmosiderin in the liver, spleen. kidneys, bone-marrow and other organs, a fact which will be referred to later.

Hæmatin, the iron-holding radicle of hæmoglobin, constitutes about 4 to 5 per cent. of the latter substance, which therefore consists mainly of the protein, globin. Hæmatin is a " porphyrin," one of a series of substances composed of various pyrrol groups with side-chains and capable of taking up metals such as iron, copper, etc. It is a brown, non-crystallisable substance, which may occur either in reduced or in oxidised form. In the tissues, as noted on p. 223, it is readily split up into an iron-free constituent, hæmatoidin, and an iron-containing part, hæmosiderin.

Hæmatoidin, the iron-free constituent of hæmatin, is apparently identical with bilirubin or bile-pigment, and is usually excreted by the liver. If not carried to that organ it may, however, slowly crystallise out in the form of characteristic yellowish or orange-red to dark ruby-red clino-rhombic prisms or needles (Plate XI, opposite p. 222, Fig. 1), though it may also be found in the form of irregular masses or granules. Its formation has been said to occur independently of cell-activity, but Rich (1924, 1925) has shown in tissue-culture and Muir and Niven (1935) have also demonstrated by animal experiment, that hæmatoidin is formed within cells, apparently being separated from the hæmosiderin-fraction intracellularly. These observers saw in their experiments no evidence of extra-cellular formation of hæmatoidin. Whilst it is certainly formed within cells, it may later be deposited in the tissues, sometimes in association with fat-globules. It is found especially at the sites of old cerebral or other hæmorrhages, or in thrombi in large veins, in old pulmonary infarcts, etc. When once formed, these hæmatoidin-crystals and granules are extremely resistant, and may be found in the tissues many years after their formation.

Hæmosiderin is the iron-containing part of hæmatin. In the normal process of hæmolysis, as indicated above, the iron-free hæmatoidin is eliminated in the bile, but the iron-containing fraction of the broken-down hæmatin is stored by certain cells as hæmosiderin until it is required for the production of fresh hæmoglobin. This hæmosiderin is probably in the form of hydrated ferrous oxide, more or less loosely combined with protein. The stability of this combination appears to vary in different diseases and in different organs. Hæmosiderin, when the combination is loose, is easily demonstrated by the Prussian-blue reaction (Plate XI, opposite p. 222, Fig. 3). When more firmly united with protein. the colour-reaction may be slow in appearing, the union having first to be broken up ; or, again, it may be entirely prevented when the combination is sufficiently firm to resist the separation. When unstained, the hæmosiderin-series of pigments occurs in the form of yellowish or golden-brown granules, which are present usually within the cells, though in some instances they may be deposited in the intercellular lymphatic spaces by phagocytic cells. This pigment is not found in crystalline form.

Hæmosiderin is formed by the action of living cells, macrophages, which ingest and disrupt the hæmoglobin. Hæmosiderin appears in the cells within a few hours, as compared with hæmatoidin which in experimental observations is not seen as crystals until about seven days. The presence of sufficient oxygen is said to favour the elaboration of hæmosiderin. It is formed and stored in great excess in certain pathological conditions in which hæmolysis is exaggerated, notably in Addisonian anæmia, malaria, etc. It is found especially in the cells of the liver, kidneys, spleen, and bone-marrow. In uncontrolled Addisonian anæmia with excessive hæmolysis, the deposit of hæmosiderin in the liver is sufficiently characteristic to have diagnostic value. It occurs within liver-cells in the outer portion of the lobules and around the bile-canaliculi. Pronounced deposition of hæmosiderin is found in the spleen after repeated blood-transfusions and also in patients with *Bacillus pyocyaneus* (*Pseudomonas aeruginosa* or *pyocyanea*) infections.

Changes occurring in Effused or Extravasated Blood. Hæmorrhage, or the escape of blood from the vessels, may occur into the tissues or cavities, or from the surface of the body, and is due to injury of the vessel-wall, which may be either traumatic or toxic in origin. Hæmorrhage may occur also from the heart, *e.g.*, from rupture or injury. Hæmorrhages may vary in size from those visible only by means of the microscope, up to large effusions. Among the toxic causes of hæmorrhage may be mentioned the bacterial toxins : certain chemical poisons such as phosphorus : phytotoxins or vegetable poisons such as ricin and abrin : zoötoxins or animal poisons such as snake-venom, some varieties of which contain a specific substance, an endotheliotoxin or endotheliolysin, which attacks especially the endothelium of the vessels. The hæmorrhages occurring in anæmias, leukæmias and in renal disease, are probably also due to toxic substances of as yet unknown nature and origin present in the blood ; and the hæmorrhages which occur in jaundice are due, in all probability, to lack of prothrombin from a deficiency of vitamin K (pp. 161, 442, 670–1 and 976).

The secondary changes occurring in such hæmorrhages vary considerably with their size and site, and may also be influenced by the presence of toxic substances in the blood, or by micro-organisms. When of small size, hæmorrhages are usually readily absorbed ; but, when large, such absorption may be gradual or partial, and in some cases very imperfect. The sequence of the changes in effused blood may be readily studied by injecting, with aseptic precautions, varying quantities of blood into the peritoneal cavities of animals. Coagulation may or may not occur, depending on the presence or absence of the necessary ferments and on the amount and nature of any cell-damage in the part, and also on the nature of any cells present. Small hæmorrhages may be rapidly absorbed, the fluid of the effused blood being carried off by lymphatics, and perhaps also by blood-vessels. Some of the red corpuscles may also pass directly into the lymphatics. If the effusion is of large size, however, these processes may be imperfectly carried out, and other changes then occur in the remaining mass (*see*, for example, Figs. 588–9, pp. 975–6). This may gradually become more inspissated by absorption of fluid. Coagulation need not necessarily occur, but the red corpuscles usually run together into homogeneous masses, their hæmoglobin being largely extruded. This hæmoglobin may soak into and stain the surrounding tissues, and a large part of it may be absorbed into the lymphatics and blood-vessels, carried to the liver, and excreted as bile-pigment. If large quantities of hæmoglobin are set free in this way, the kidneys will also take part in its excretion, and in such cases the hæmoglobin-derivatives appear to act as cell-poisons, and may produce cloudy swelling and other degenerative changes in the organs and tissues, and may also cause considerable local inflammatory reaction. In many cases of sterile hæmothorax, occurring during the War of 1914–18, Carnegie Dickson observed that, for weeks and even months, the extravasated blood might remain unaltered in its naked-eye characters and without coagulation, the red corpuscles also remaining apparently unaltered and well preserved in shape, size and hæmoglobin-content. This may also be seen sometimes in aged or debilitated people. For the changes in extravasated blood in subdural hæmatoma, *see* p. 974 *et seq.*

Chemical and physical changes also occur locally in the pigment of the effused blood. The hæmoglobin is split up, probably by enzyme-action, into its components, globin and hæmatin. The former is readily digested and removed, whilst the latter is further split up by enzymes into the iron-free hæmatoidin and iron-containing hæmosiderin. The granules of the latter are very slowly removed, carried to the liver and elsewhere, and stored until they can be utilised for the formation, in the bone-marrow, of new hæmoglobin. The hæmatoidin not so removed to and excreted by the liver, and therefore especially that part of it in the deeper portions of the effused blood, slowly crystallises out to form the characteristic ruby-red prisms, already described in this chapter. In large hæmorrhages, where the absorptive changes are very slow or imperfect, hæmatin, or even the original hæmoglobin, may remain intact, and crystallise out. Hæmatoidin is, however, of much more frequent occurrence, and, as already noted, may persist for many years in the remains of old blood-clots (Plate XI, opposite p. 222, Fig. 1). Another important and very insoluble constituent of the red corpuscles, viz., cholesterol, may also crystallise out, and its characteristic rhomboidal plates (Fig. 99, p. 202) may be found in old hæmorrhages.

Phagocytosis in and around blood-effusions is a subject which is to some extent dealt with elsewhere (p. 32). Both red corpuscles, and the granules and crystals of pigment derived from their disintegration, may be extensively taken up by various phagocytic cells, more especially by the macrophages, described in the section on phagocytosis (p. 32). Ingested red corpuscles disappear rapidly within the digestive vacuoles of these cells, leaving some pigment-granules in the cytoplasm as a residue. These phagocytic cells may then migrate and deposit their contained pigment elsewhere. They tend to pass along the lymphatics, and are arrested in the lymph-nodes, where they may deposit their contents; or, perhaps more commonly, are themselves englobed by the actively phagocytic cells which line the lymph-sinuses of the nodes, this often leading to extensive pigmentation of these organs. The pigment-particles may be found also in the endothelial cells lining lymphatics, and in the connective-tissue and other cells in the neighbourhood; or they are carried even to distant parts of the body. This pigment may persist for very long periods; and ultimately the remains of such a hæmorrhage may show as brownish or brownish-red pigment-granules or crystals and debris, surrounded by proliferated fibrous tissue.

Blood effused into certain organs or tissues may undergo special changes. For example, in gastric hæmorrhage, the blood becomes brownish—the so-called "coffee-grounds" appearance—from the action of the gastric juice—the brown colour being due to the splitting up of the hæmoglobin into hæmatin and globin ; or the effused blood may be blackened by the action of sulphuretted hydrogen, *e.g.*, in the stomach, and more especially in the intestine, leading to the condition known as **melæna** or the presence of black altered blood in the stools. Not only submucous intestinal hæmorrhages but also small subserous hæmorrhages on the outside of the intestine and elsewhere in the peritoneal cavity are frequently seen *post mortem* as small black spots, due in a similar way to the production in them of sulphide of iron.

Hæmoglobinuria. In certain diseases characterised by rapid and extensive destruction of red corpuscles, more hæmoglobin may be freed into the blood than can be dealt with and transformed into bilirubin by the liver. In such cases the kidneys may excrete part of the hæmoglobin, the resulting urine being dark brownish-red, brown or even almost black in colour—the condition of hæmoglobinuria. This condition is seen typically in hæmoglobinuric or "black-water" fever, and also in paroxysmal hæmoglobinuria (pp. 223 and 659 *et seq.*). On spectroscopic examination of the urine from such cases, the typical absorption-bands of hæmoglobin, and sometimes of methæmoglobin, are found.

Methæmoglobinuria. Methæmoglobin is a ferric compound containing half the oxygen of hæmoglobin and it is produced readily from reduced hæmoglobin. The action of reducing agents favours its occurrence. Certain chemicals, such as phenacetin, acetanilide, sulphonamide and its relatives ("prontosil," etc.—which may also produce sulphæmoglobinæmia), chlorates and nitrobenzol, if taken in excess, may cause the formation of methæmoglobin. It is found also in some bacterial infections such as those due to streptococci and pneumococci and it may be present in the blood in pneumonia. If excess is present, it may appear in the urine, giving it a dark colour—methæmoglobinuria. It may be identified spectroscopically.

Porphyrinuria (previously often known as "**Hæmatoporphyrinuria**"), the presence of "hæmatoporphyrin" or, better, **uroporphyrin,** or simply **porphyrin,** *i.e.*, iron-free hæmatin, in the urine in excessive quantities, is a rare condition, found most typically, in certain individuals, after the administration of large doses of sulphonal or trional, or of members of the sulphanilamide-series of drugs and certain related nitro- and amino-compounds, as well as in industrial poisoning with **methyl-chloride**—a gas used in some domestic refrigerators. These substances act probably upon the liver and interfere with the normal breaking-down of hæmoglobin. The urine becomes of a dark port-wine colour, and shows the absorption-bands of porphyrin spectroscopically. In these disorders, porphyrins (as the so-called "coproporphyrins") are also excreted in the fæces. More rarely, porphyrinuria may be congenital. Evidence is accumulating to show that this substance may be the basis for the excessive sensitivity of the skin to light and ultra-violet rays which some individuals exhibit, as in the disease **xeroderma pigmentosum,** for the porphyrins are photodynamic agents in animal tissues.

Hæmochromatosis is a rare disorder, commonest in middle-aged males. It is characterised by widespread pigmentation of certain glandular and other organs and tissues, particularly the liver (Fig. 432, p. 774) and pancreas, in which organs it is accompanied or preceded by cirrhotic and atrophic changes (pp. 774, 793 and 804). It also affects the adjacent lymph-nodes ; parts of the alimentary canal : and the muscular tissues of the heart and blood-vessels. In the liver, a not uncommon complication is the supervention of multicentric carcinoma ; whilst in the pancreas, the lesion may or may not give rise to glycosuria. The skin usually, though not invariably, becomes the seat of extensive melanosis, a phenomenon which, when combined with the presence of glycosuria, led to the application of the term "diabète bronzé"—"bronzed diabetes"—to such cases. The dull-bluish or leaden hue of the skin, seen especially in the later stages of the disease, is due to the deposition of hæmosiderin in the corium, more particularly in and around the sweat-glands. For a note of the changes in the central nervous system, *see* pp. 1070–71.

The cause of hæmochromatosis is unknown. The pigment which is present is mainly hæmosiderin, but there is also "hæmofuscin," which does not give reactions for iron. Although there is an excessive deposit of hæmosiderin in the tissues, there is little evidence of hæmolysis and no excess of iron in the blood. For some unexplained reason, iron accumulates in the tissues often in enormous amounts. Mallory (1925) produced in rabbits a condition resembling hæmochromatosis by administering excess of copper to them, and he suggested chronic copper-poisoning as a cause of the condition in the human subject, but there is no satisfactory evidence that this is so and certainly no excess of copper is found in the condition in man.

The degenerative and fibrotic changes that occur in the organs, especially the liver and pancreas, may be due to an unknown damaging factor, or may be secondary to the excessive deposit of the pigment. The glycosuria or "diabetes" is a late secondary result of the pancreatic lesion. The testes usually show considerable hypoplasia or atrophy.

Note on Malarial Pigmentation. Several varieties of pigment may be distinguished.

1. A very dark-brown pigment, known as "hæmozoïn," often described as being "black" in colour, elaborated by the parasites from the hæmoglobin of the red corpuscles which they infest. This pigment occurs in granules, and is the specific colouring-matter which gives the characteristic naked-eye and microscopical peculiarities to malarial organs and tissues. It appears probable that the parasite, in the process of its growth, feeds upon the protein globin-radicle of the hæmoglobin of the corpuscles, the hæmatin part not being assimilated, but altered in some way and left as a by-product, which may or may not have any special function in the life of the parasite. This pigment, formed by the specific activity of the parasite, may be found, sometimes in enormous quantities, within phagocytic cells, especially the large mononuclear cells and the endothelium of vessels, and in the phagocytic cells of the spleen, liver, and bone-marrow; and, less frequently, lying free in the lymphatic spaces. It is insoluble in strong acids, soluble in alkalies, and readily dissolved by ammonium sulphide. Sinton and Ghosh (1934) state that it resembles hæmatin in its physico-chemical characters. In fatal cases of malaria, the capillaries of the cerebral cortex may be plugged with parasitised red corpuscles and granules of pigment, affording a striking demonstration of the specific pigment produced by the organisms.
2. Yellow pigment formed from the hæmoglobin of broken-down red corpuscles. This is a product of hæmolysis, and occurs in the cells of the various organs and tissues, and from it there may be produced :—
3. Bile-pigment and urobilin. If the elimination of the bile-pigment so formed is deficient, jaundice will result.

"HEPATOGENOUS" PIGMENTATION, ICTERUS, OR JAUNDICE are terms applied to the conditions characterised by the presence of bile-pigment, usually in solution in the body-fluids, whereby the tissues are permeated and in a certain sense "stained" by the yellow or greenish-yellow biliary pigments. As already stated, bilirubin, the most important of these biliary pigments, is isomeric with hæmatoidin, and is derived from the destruction of effete red corpuscles in the process of hæmolysis. Bile-pigment, being soluble in alkaline watery media, is, in such cases of jaundice, for the most part in solution in the blood and lymph, the tissues being thus permeated, as it were, but not necessarily actually stained, during life at all events, by the yellow or greenish-yellow solution ; though certain of the tissue-elements, *e.g.*, connective-tissue fibres, do become bile-stained during life, others, for example, muscle-cells and fat-cells, undergo staining only after death.

When jaundice becomes more advanced, however, the pigment may be deposited in granular form, a condition which is seen especially well in the liver, and to a less extent in the kidney-cells, *e.g.*, in cases of severe obstructive jaundice. In old-standing cases of jaundice, the original yellow or greenish-yellow tinge in the skin may gradually be replaced by a dark olive-green or even by a dark brownish-green colour, produced apparently by a slow oxidation of the bilirubin.

Part of the excess of the bile-pigment and bile-acids is excreted in the urine by the kidneys, and these organs are specially liable to be extensively damaged, albuminuria being a frequent accompaniment of severe jaundice.

Types of Jaundice and Mechanism of Production:—Van den Bergh Test. It is convenient to refer to this test first, as its application has helped to elucidate certain points in the problem of jaundice. The substance used for the test is Ehrlich's diazo-reagent, which gives a violet colour with bilirubin, and the following types of reaction occur when the reagent is applied to the blood-serum : (*a*) Direct (and immediate), and (*b*) Indirect (or delayed), in which it may be necessary to add alcohol to get the colour. The direct reaction is given by bilirubin which has passed through the liver-cells and the indirect (or delayed) occurs with bilirubin which has not been acted upon by the liver. The difference in reaction is due, not to any difference in the bilirubin as such, but to the adsorption of the bilirubin to the plasma. Pure bilirubin at the *p*H of blood gives a direct van den Bergh reaction, but, if normal plasma be added, the reaction becomes indirect owing to adsorption. Bilirubin which has passed through the liver-cells becomes mixed with bile-salts and a variable amount of cholesterol ; these substances lower the surface-tension and prevent adsorption of bilirubin to plasma, and thus a direct reaction occurs. Therefore, if whole bile gets into the blood, as in the obstructive type of jaundice, a direct reaction will be given, but if bilirubin is present in excess in the blood, as in excessive blood-destruction—giving hæmolytic jaundice—an indirect reaction is found. It not infrequently happens that bilirubin in both states is present in the blood and then a bi-phasic reaction is the result, *i.e.*, a direct, followed by an indirect, reaction ; also, in individual cases, anomalous reactions are obtained which are difficult to interpret.

Bilirubin, the essential pigmentary factor in jaundice, is formed from hæmoglobin by the action of cells of the reticulo-endothelial system wherever these occur in the body, including the von Kupffer's cells of the liver itself. Normally the bilirubin is carried to the liver, passed through the liver-cells and excreted by the bile-capillaries and so reaches the intestine, some being temporarily stored in the gall-bladder.

Jaundice, or icterus, may occur from a breach in this normal mechanism at several points : (*a*) The liver-cells may be damaged, but not actually destroyed, and they fail to deal with the bilirubin, which thus accumulates in the blood. (*b*) An excess of bilirubin may be formed. If the liver-cells are normal they can deal with this, and no jaundice occurs. But if damaged, or undeveloped (as in the new-born), they will fail to deal with this excess which, therefore, accumulates as in (*a*). (*c*) The liver-cells may be destroyed and the bile in them set free into the circulation. And (*d*) the bile-outflow may be blocked and the bile-capillaries burst into the tissue-spaces, eventually liberating bile into the blood.

In addition to testing for the amount and character of bilirubin in the blood, it is necessary to examine the urine and fæces. In obstruction—(*d*) above—the urine contains bilirubin and bile-salts and the stools have a decrease in urobilin (= reduced bilirubin) owing to failure of bile to reach the intestine.

Where there is jaundice without obstruction, the urine and stools show increased urobilin from the excess of bilirubin in the blood and the absence of impediment to outflow of bile to the intestine *viâ* the bile-ducts.

On the basis of its causation, McNee [1] makes the useful classification of cases into : " **obstructive hepatic jaundice,**" " **toxic and infective hepatic jaundice,**" and " **hæmolytic jaundice.**" **Obstructive jaundice** may be caused by blockage of the ducts, either in the liver, or the common duct, *e.g.*, by calculi, cholangitis, parasites, tumours, or by pressure on the ducts, *e.g.*, by enlarged lymph-nodes at the hilum of the liver, tumours of the head of the pancreas, and, rarely, by aneurysm of the hepatic artery.

Toxic (and **infective**) **jaundice** also may be due to many agencies, *e.g.*, chemical poisons such as chloroform, phosphorus and trinitrotoluol (T.N.T.) : or to infections of bacterial or other origin, especially to severe septicæmias, yellow fever and Weil's disease or infectious jaundice due to *Leptospira icterohœmorrhagiœ.*

Hæmolytic jaundice is seen in excessive blood-destruction (pp. 656, 658 *et seq.*). With this there is practically always associated some depression of liver-cell function. It occurs as " hæmolytic " or " acholuric familial jaundice " (pp. 656 and 658), in which the red corpuscles are unduly fragile (pp. 586–7) : and in severe anæmias such as uncontrolled Addisonian anæmia : and in malaria and blackwater fever (p. 659).

A. R. Rich [2] has pointed out that this division of jaundice into the above three headings raises various difficulties owing to overlapping of the types ; and he suggests that " from the standpoint of the clinical and pathological evidence, cases of jaundice are separable, on the basis of pathogenesis, into two main types. The first type, **retention jaundice,** results from overproduction of bile-pigment, usually associated with conditions (anoxæmia, fever, immaturity) which tend to render the excretory power of the liver subnormal ; enough bilirubin is therefore retained in the blood to stain the tissues. This form of jaundice is characterised clinically by (1) indirect-reacting plasma bilirubin ; (2) increased amounts of fæcal urobilin ; and (3) urobilinuria. Pathologically, the ducts are patent, but the liver-cells may show atrophy or cloudy swelling, depending upon the associated condition of which the jaundice is a symptom.

" The second type, **regurgitation jaundice,** is caused by the reflux of whole bile from the canaliculi into the blood-stream. This type is characterised clinically by (1) direct-reacting plasma bilirubin, (2) subnormal amounts of fæcal urobilin, and (3) the presence of bilirubin and bile-salts in the urine. The pathological basis of this form of jaundice is rupture of the canaliculi resulting from obstruction of the ducts, or from necrosis of the hepatic cells.

" Combined forms may occur, as well as a transition from one of these types of jaundice to the other."

Retention-jaundice thus includes the " hæmolytic " form and some of the forms of " toxic " jaundice of McNee's grouping ; while regurgitation-jaundice includes the " obstructive " group and some of the severe " toxic " forms, *e.g.*, acute liver-atrophy.

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[1] *Quart. Jour. Med.*, 1923, **16**, 290. McNee makes this classification on " the view that the polygonal glandular cells are not essentially concerned with the manufacture of bile-pigment, but transfer it from vascular-capillaries to bile-capillaries."

[2] *Bull. Johns Hopkins Hosp.*, 1930, **47**, 338–377.

The profound toxic effects of jaundice are to be regarded as due, not so much to the presence of bile-pigment, as to the action of the accompanying bile-salts, which produce cloudy swelling, hæmorrhages and other cytolytic phenomena, bradycardia, coma and death.

III. PIGMENTARY SUBSTANCES OF EXTRANEOUS ORIGIN—EXOGENOUS PIGMENTATION

Substances introduced into the body from without may produce alterations in the colour of the tissues, either because of these substances themselves possessing definite colour, or because they may stain, or may form coloured compounds with, the tissues or with certain of the tissue-elements.

Such substances may obtain entrance into the body by means of the respiratory passages or the alimentary canal, or through the skin.

(*a*) **Pneumonokonioses (Dust-Diseases), or Pigmentation due to Inhalation of Foreign Particles** (p. 542 *et seq.*). The lungs of newly-born infants, and also those of persons who live in regions where dust and smoke are absent—*e.g.*, Laplanders—are pink in colour, and do not show the presence of particles of carbon, stone-dust, etc., seen so commonly in these organs as to be regarded as almost a normal condition, more especially in city-dwellers or in workers exposed to dust by the nature of their occupation. Minute particles of soot, coal, stone, etc., suspended in the air in the form of dust, are inhaled into the respiratory passages. The greater part of this dust comes in contact with, and adheres to, the moist mucous surfaces of the nose, pharynx and trachea, and larger bronchi, and is carried out by the secretions of these passages. If in excessive amount, however, some of the particles may be carried further into the lungs, and perhaps even as far as the ultimate air-vesicles, though most of them are probably caught on the moist walls of the smaller bronchi. The particles are then englobed by phagocytic cells (*see* Plate XI, Fig. 6, facing p. 222)—and these, if not carried out by the ciliary movements of the cells lining the bronchi and expectorated in the sputum, may migrate into the lymphatic spaces and along the lymphatic channels of the fibrous-tissue framework of the lungs, carrying with them their contained pigment. This they may deposit in the lymph-spaces of any part of the fibrous framework, for example, in the peribronchial and perivascular tissue, and in the interlobular septa, especially where these join the deeper layer of the pleura, thus tending to demarcate the outlines of the lobules, and producing a somewhat polygonal network of pigment which may be seen shining through the transparent serous layer of the pleura. Some of the pigment is also usually carried to the bronchial and to other groups of lymph-nodes, which act as filters for the lymph-stream. This pigment, especially if in excessive quantity, may act as a chronic irritant, and produce a gradual proliferative increase of the fibrous tissue of the lung.

In the case of coal-miners and others exposed to an excessive amount of coal-dust in the air they breathe, this pigmentation of the lungs may become extreme, and is known as **Coal-miners' Lung,** or **Anthracosis,** from the black colour of the organs (p. 542–3 and Fig. 318). The bronchial lymph-nodes of such cases usually become deeply pigmented; and the pigment may be found also in more distant groups of nodes, and even in the spleen and liver, and lymphatics of the peri- and epi-cardium, diaphragm, and elsewhere.

The inhalation of fine particles of stone-dust produces similar, but usually more marked and severe, results, the irritation and proliferative changes being pronounced. The condition is known as **Silicosis, Chalicosis,** or **Stone-mason's Lung** (p. 543), and frequently, though not necessarily, is combined with, or leads to invasion of the diseased tissues by, tuberculosis.

Asbestosis. This is really a form of silicosis, as the asbestos-fibrils are mainly magnesium silicate. They occur in the fine dust in works where asbestos is being prepared from the crude mineral to be woven into heat-insulating material. The lesions are produced by inhalation of these fibrils and take the form of a diffuse fibrosis, more especially in the lower lobes of the lungs, in which areas the characteristic " asbestos-bodies " can be found (Figs. 326–8, pp. 547–8). These bodies may also be found in the sputum.[1] (*See* Respiratory System, pp. 546–8.)

Other forms of these pneumonokonioses may be produced in **Iron-** or **Steel-Grinders (Siderosis)**, workers in vermilion, feathers, etc. In the case of grinders, the stone-dust produced from the grindstone, rather than the fine particles of metal, plays the chief part in the production of this form of the disease.

Of recent years it has been recognised that the main cause of fibrosis in the " dust-diseases " mentioned is the presence of the **silicon-compounds** which the dusts contain. Pure carbon excites little or no fibrosis and by itself is innocuous. But, if combined with silica, there is definite, often extensive, fibrosis. Such combination of carbon-pigment *plus* silica is called **Silico-Anthracosis.** Much the same relationship applies to iron-pigmentation ; it is the associated silica that causes the fibrosis, whilst the iron, *e.g.*, in **Hæmatite-Miners,** is deposited in quantity in the fibrosed lung, often giving it a brick-red colour. The fibrosis caused by the silica impedes the lymphatic drainage and thus facilitates the accumulation of accompanying pigment.

All forms of silica are not equally harmful. According to Jones,[2] " Sericite " —a hydrated aluminium and potassium silicate— is specially dangerous. It occurs in minute crystals, often difficult to identify in the tissues. Kettle and others [3] have shown **experimentally** that the action of silica is not merely mechanical, but by its slow solution has a necrosing effect on the tissues. Irritant substances which are insoluble, such as carborundum, do not produce necrosis, and their irritant effect is not so obvious. The necrosis produced by the various forms of silica makes a favourable nidus for the growth of organisms, *e.g.*, when tubercle bacilli are inoculated intravenously, following a local injection of silica. The bacilli are carried to and settle in the damaged area and multiply there. The siliceous particles are taken up by reticulo-endothelial cells, cause necrosis and excite fibrous proliferation. Further, in the case of kaolin (a silicate in china-clay), we have found that, if **inhaled** for long periods by guineapigs, it produces fibrosis, but Kettle [4] found that when it was **injected** intra-tracheally in guineapigs it accumulated in the air-alveoli without producing any characteristic fibrosis ; but, if dead tubercle bacilli were injected along with the kaolin, typical fibrous nodules were formed, with the bacilli in their centre. This raises the question as to whether the fibrosis due to inhaled irritant particles is not frequently the combined result of infection *plus* dust. That a fibrosed lung is of itself a vulnerable area is, however, fairly well established, and is thus liable to attack by tuberculosis superimposed upon an older dust-fibrosis.

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[1] W. E. Cook and S. McDonald, *B.M.J.*, 1927, ii, 1024, 1025; M. J. Stewart and A. C Haddon, *Jour. Path. and Bact.*, 1929, **32**, 172.

[2] *Jour. of Hyg.*, 1933, **33**, 307.

[3] *Jour. Path. and Bact.*, 1932, **35**, 395.

[4] *Ibid.*, 1935, **38**, 201.

The cause of death in cases of silicosis is frequently the associated or superadded tuberculosis which often causes extensive destruction in such a lung. Gangrene of the lung may occur and prove fatal. The extensive fibrosis of itself may so reduce the available lung-tissue as to cause extreme dyspnœa. The right side of the heart in such cases becomes greatly hypertrophied but may ultimately prove unable to keep up an adequate circulation through the lungs, and death from failure of the right ventricle ensues.

(*b*) **Pigmentation Produced by Substances Introduced by the Alimentary Canal.** In this instance, the substances may be absorbed in solution ; and later, on being carried to the tissues, may become altered in such a way as to produce pigmentation, for example in **argyria** or **chronic silver-poisoning,** which may supervene in cases where soluble silver salts are administered for a prolonged period. Particles of the insoluble albuminate of silver are deposited in the skin, especially in the connective tissue around the sebaceous and sweat-glands : and also in the liver, bone-marrow, and kidneys, more particularly in the glomeruli, and in and around the straight tubules. In the case of the skin, the pigment may, under the action of light, assume a slate-grey or even a dark bluish-purple colour.

Argyria may result from the introduction of silver-compounds otherwise than by the alimentary canal, as by absorption from the conjunctival sac, the upper respiratory tract, or the urogenital mucosa. Whilst the salts of silver, such as the nitrate, produce this condition more rapidly, the long continued use of colloidal-silver preparations is not without danger of argyrosis.

In like manner, the prolonged ingestion of small quantities of **arsenic,** either medicinally or as an impurity in beer or other article of diet, may lead to considerable pigmentation of the skin. Here, however, the mechanism is different. Whilst arsenic is deposited in the skin and hair, the characteristic pigmentation of chronic arsenical poisoning is due largely to melanin—producing an irregularly distributed melanoderma—and not to a pigmented arsenical compound. In **chronic lead-poisoning,** the characteristic " blue line " on the gums along the roots of the teeth is due to the formation of lead sulphide, and is most in evidence where attention is not paid to cleanliness of the teeth.

(*c*) **Pigmentation due to Foreign Particles introduced through the Skin.** The best example of this is in tattooing, where insoluble pigmentary substances such as carbon (*e.g.*, in the form of gunpowder, or Indian or Chinese ink), Prussian-blue, or vermilion, are introduced intentionally through small punctured wounds in the skin. In such cases some of the pigment may be carried by phagocytes and deposited in neighbouring lymph-nodes. Similar pigmentation may follow from the penetration of unburned grains of gunpowder in explosions, or from the firing of blank cartridge. In persons following certain occupations, *e.g.*, miners, chimney-sweepers, engineers, and others, from lack of proper attention to cleanliness or from injury, dirt-particles may become rubbed into or " ingrained " in the skin.

(*d*) **Pigmentation due to Parasitic Fungi.** Pigmentation, or, more accurately, discoloration of the skin and mucous membranes, may be produced by certain coloured parasitic fungi : for example, one of the black moulds, *Mucor niger*, which causes a black discoloration of the lingual papillæ. In thrush, white patches are produced on the buccal mucous membrane by *Oïdium* (or *Monilia*) *albicans*. Some of the coloured *Aspergilleæ* are also sometimes pathogenic in man—for example, *Aspergillus niger*, the cause of aspergillar mycosis, which most frequently attacks the outer and middle ear, nose and mouth. *Microsporon furfur*, which causes pityriasis (or tinea) versicolor, produces a brown or brownish-yellow discoloration of the skin.

POST-MORTEM CHANGES

Under this heading may be classified the occurrence of rigor mortis : softening of the tissues from autolysis and from putrefaction : post-mortem discoloration of the tissues, gas-production, etc.

These changes are of importance in Forensic Medicine and are referred to in greater detail in works on that subject.

Rigor mortis is a stiffening of the dead body, due to the hardening and shortening of its muscular tissues. It is said to supervene first in the muscle of the heart, but the earliest superficial evidence of it is usually to be found in the muscles of the face, the rest of the body becoming involved from above downwards, and the condition tending to pass off again in the same order. The cause of the phenomenon is the coagulation of the muscle-proteins. The period after death at which rigor mortis may supervene is extremely variable, and depends upon many factors, such as the duration and nature of the illness preceding death. It is also influenced by the temperature of the environment, heat accelerating, cold retarding, its appearance. If a body is frozen immediately after death, rigor mortis will not occur until the body has been thawed. It appears usually in from one to seven hours after death, and may pass off in a day or two. In cases of tetanus, or of strychnine poisoning, and in some of the acute infective fevers, it may supervene almost immediately after or even before actual death has taken place. It occurs also very rapidly in individuals dying after severe muscular exertion, owing possibly to the large amount of lactic acid present in the muscles ; and it is usually more pronounced in muscular individuals than in those who are ill-developed or wasted. In other conditions, *e.g.*, death from hæmorrhage, its appearance may be greatly delayed, or it may be slight, or even absent. As a general rule, the more rapid its onset, the more quickly does it disappear, and *vice versâ*. In all probability its disappearance is due to the softening of the myosin-clot under the action of autolytic ferments, a subject which will be discussed later.

Post-mortem Softening of the Tissues. This process may be brought about by two sets of substances, viz., the bacterial ferments and the autolytic tissue-enzymes ; and it may be inhibited by destroying or preventing the development of these substances, *e.g.*, by heat, or by chemical preservatives such as formalin, corrosive sublimate or alcohol.

The normal processes of **putrefaction** which supervene in dead organic matter consist in the splitting up of the more complex into simpler chemical substances by the agency of the bacteria of putrefaction. These act upon the tissues by means of proteolytic and other digestive ferments, the processes being in many ways similar to those of animal digestion.

Putrefactive processes may take place with great rapidity after death, and are aided by warmth, moisture, and the ready access of putrefactive organisms. They occur early in cases of death from septicæmia and where the organisms enter the blood-stream and tissues before death. These organisms are always present on the surfaces of the body and in certain parts of the alimentary canal, especially the mouth and intestines ; and putrefactive changes are generally found first in these regions, and particularly in the abdomen.

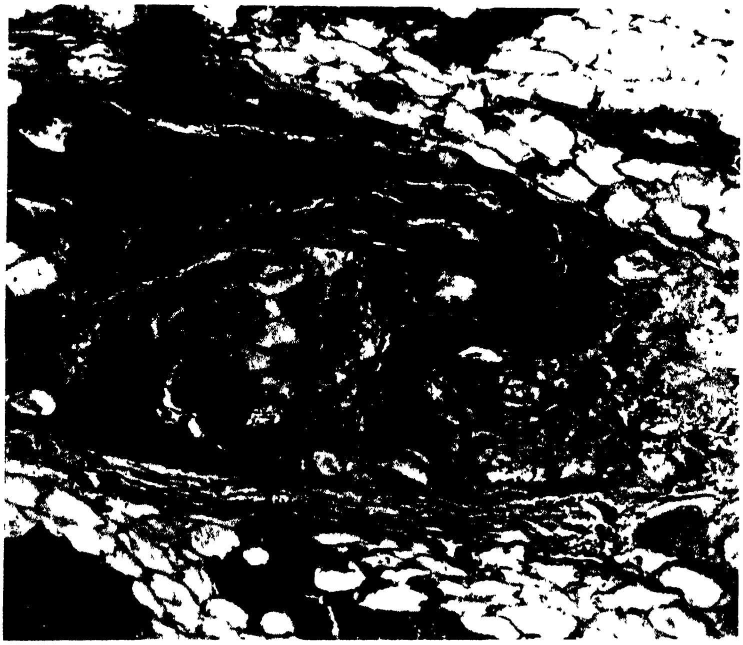

FIG. 110. Post-mortem digestion of pancreas. Much of the normal structure of the pancreas has disappeared, being replaced by granular debris and irregular spaces. Portions of undigested pancreas and adipose tissue are seen around the periphery of the field. There is neither cellular infiltration nor vascular reaction around the autolysed area ; compare with acute hæmorrhagic pancreatitis (p. 795, Figs. 452 3). × 75.

Putrefaction is usually accompanied by the production of gases such as sulphuretted hydrogen, which may act upon the blood present in the tissues, and produce certain colour-phenomena referred to in the next section. Gas-bubbles are also frequently found in the vessels, for example on the surface of the brain. These are due to decomposition-products, and should not be mistaken for air-embolism (p. 168–9).

Autolysis of the tissues after death occurs also from the action of certain ferments which are developed from the tissues themselves, quite apart from the presence of bacteria. Thus, if pieces of tissue are incubated under aseptic precautions, they become softened and disintegrated from the action of these autolytic ferments, the earlier stages of the process very much resembling what is seen in cloudy swelling and in necrosis. The phenomenon known as the " ripening " of meat, and also the disappearance of rigor-mortis in muscle, appear to be due to the action of these autolytic ferments, and occur even if bacterial action is prevented, *e.g.*, by suitably lowering the temperature.

While discussing these post-mortem autolytic phenomena, mention may also be made of what is known as post-mortem digestion of the stomach, the wall of which organ may, after death, become extensively thinned and even perforated by the action of the gastric juice, especially if death has occurred during active digestion. A similar post-mortem auto-digestion by means of the normal ferments of its own secretion is specially liable to occur in the pancreas (Fig. 110).

The naked-eye and microscopical alterations produced in the tissues by these bacterial and autolytic ferments must be constantly borne in mind in the examination of post-mortem material, and it is sometimes difficult to differentiate between these alterations and the changes produced by bacterial and other toxins in disease, both conditions being often combined in varying degree.

For descriptions of the putrefactive changes which occur in the intestines during life, *e.g.*, the production of indole, skatole, sulphuretted hydrogen, etc., reference should be made to works on Bio-Chemistry ; similarly, descriptions of the series of decomposition-changes which occur at various periods after death will be found in text-books on Medical Jurisprudence.

Gas-production in the Organs and Tissues. Reference has already been made to the production of sulphuretted hydrogen by putrefactive bacteria in the alimentary canal. Gas may also be produced in the tissues by the action of special gas-forming organisms, *e.g.*, *Bacillus welchii* (*Clostridium welchii*), *Vibrion septique* (*Clostridium œdematis-maligni*), etc. (*see also* pp. 252–5).

Post-mortem Discoloration of the Tissues. When blood-pigment is extensively liberated from the red corpuscles by putrefaction, it may soak out through the vessel-walls and stain the neighbouring tissues. After death from septicæmic diseases, this usually occurs very early, and the cutaneous veins may frequently be seen marked out on the surface of the body as reddish or greenish-red lines. Similarly, the tissues and organs, *e.g.*, the liver, spleen, kidneys, etc., may show a diffuse red staining ; and a like phenomenon may be observed in the endocardium and inner coats of the aorta, pulmonary and other vessels. It should be noted, however, that such diffuse blood-staining may occur from blood-destruction in toxic and septicæmic cases, quite apart from post-mortem decomposition.

As long as the blood remains fluid after death, it is capable of accumulating in the veins and capillaries of dependent regions of the body under the influence of gravity and will give an increased colour, which may be bluish or reddish purple, to such areas. This redistribution of the blood, which is lacking in areas pressed upon by the weight of the body, is called **post-mortem**

hypostatic congestion. In Forensic Medicine it is frequently of importance in determining the position of the body during the first few hours after death. The various discolorations of the surface of the body which may occur after death are grouped under the general terms of **post-mortem lividity** or **livores mortis** (the " livid blotches of death ").

The greenish post-mortem discoloration frequently seen in the skin, usually commencing over the abdomen, is due to the action of the sulphuretted hydrogen, liberated during putrefaction, upon the still undecomposed hæmoglobin of the blood. Similarly, the dark slate-blue, dark greenish, or almost pure black discoloration (pseudomelanosis) often observed on the surface of the abdominal organs, and even penetrating their substance for a considerable depth, especially in the case of the liver and spleen, is due to sulphuretted hydrogen, generated in the intestines, acting upon the iron of the hæmoglobin after that pigment has been broken up, the black sulphide of iron being formed.

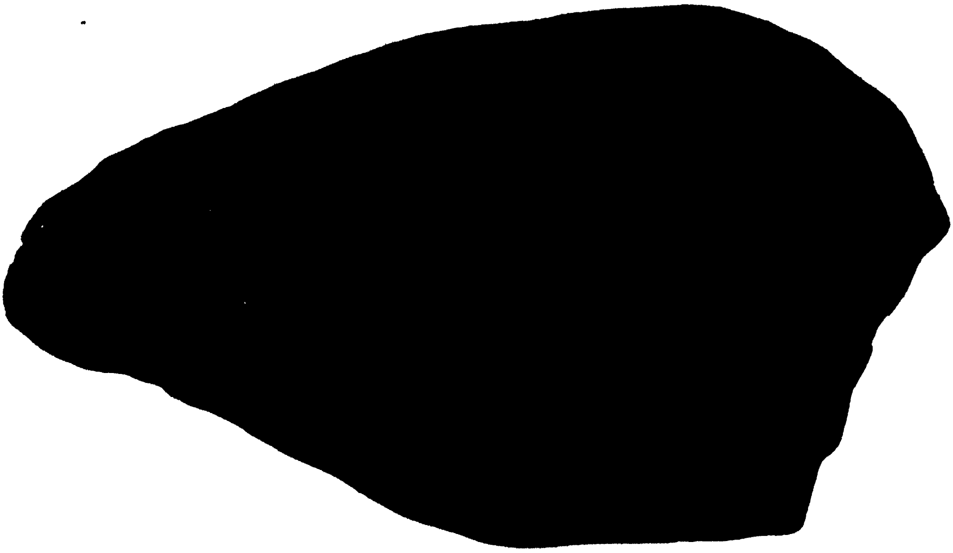

Fig. 111. " Foamy liver." The organ is riddled with numerous cyst-like spaces, due to formation of gas by putrefactive organisms.

In certain circumstances this black or greenish-black discoloration may occur during life, *e.g.*, round inflammatory, and especially round and in gangrenous, foci or areas.

DISTURBANCES OF CALCIUM-METABOLISM

Introductory Note. Under normal conditions, calcium to the amount of a half to one gramme per day is an essential need of the body. It is obtained from foods such as milk, milk-products and green vegetables. Absorption takes place from the small intestine, and, if the acidity is increased, soluble salts are formed and absorption occurs readily. On the other hand, if the bowel-contents are unduly alkaline, insoluble salts are formed and absorption is hindered. Vitamin D (p. 440) is also essential for the proper absorption of calcium. Calcium is present in the blood-plasma, and hence also in the blood-serum, in the proportion of from 10 to 11.5 mgr. per 100 cc. of blood. A small part of this is in solution, part is loosely combined with the plasma-proteins and the remainder is dissolved by some action of the parathyroids. Further, for satisfactory absorption an adequate proportion of phosphorus—probably as inorganic phosphate—is necessary, and this again depends on the vitamin-D content of the food. Thus, in order to obtain a properly balanced calcium-content of the blood, there must be a correct calcium-phosphorus ratio, for, if the phosphate-intake is unduly high, insoluble salts such as $Ca_3(PO_4)_2$, are formed and calcium-loss occurs. To sum up : The corect calcium-content of the blood is dependent on the following factors :—

1. The amount absorbed by the intestine.
2. The efficient control by the parathyroids.
3. The vitamin-D content of the food and action of available sunlight.
4. The requisite proportion of phosphorus.

The protein-content of the plasma is important, for if, from any cause, this is diminished, the amount of dissolved calcium is decreased.

Calcium is excreted mainly in the fæces : to a much less extent in the urine. Calcium is laid down in bone, the spongy part of which is the main storehouse of it in the body. Here again phosphorus in appropriate proportion is necessary. By the action of the ferment phosphatase present in ossifying areas—and produced possibly by the osteoblasts —calcium phosphate is deposited. Other minerals, such as lead, arsenic, mercury and radium, may be similarly stored in bone—and liberated therefrom by the same mechanism as that which liberates calcium. Calcium is mobilised for use by the action of the parathyroid hormone.

The **functions of calcium** in the body are several—to give rigidity to the bony skeleton : to act as a basic substance in maintaining the acid-base equilibrium : to decrease nerve-irritability : to act as a factor in coagulation of blood. It is also concerned in regulating the heart-rate.

Calcification (Calcareous Degeneration, Calcareous Infiltration, Petrifaction)

As a retrogressive change, calcification is found commonly as a sequel to other degenerative conditions. It is characterised by the deposition in cells or tissues of insoluble salts of calcium, especially the phosphate and carbonate, in proportions similar to those found in normal bone. Other minerals, such as magnesium, may also be present in smaller amounts.

Calcification often takes place in degenerated, dying or dead tissues within the living body. In old age, calcification of the costal and laryngeal cartilages and of the coats of the arteries is common, and to a certain extent may be regarded as a normal senile change ; but in some individuals, as the result of increased strain or from chronic inflammatory or other causes, the process takes place abnormally early, or to an excessive degree. Its occurrence, with the production of corpora arenacea, in the choroid plexuses of the lateral ventricles (p. 1122 *et seq.*) and in the pineal body is also a normal phenomenon with advancing age (p. 848) ; and it may occur at any age in a weakened and damaged tissue—especially in fibrous tissue—which has been the seat of inflammatory or degenerative changes, for example in the coats of blood-vessels which have been attacked by atheroma or other form of arteriosclerosis ; and similarly it may be found in heart-valves which have been subject to long-continued abnormal strain, or which have been the seat of chronic endocarditis. In the vessels it may also follow hyaline degeneration.

Calcification may be found in old hæmorrhages, in thrombi (*e.g.*, as "phleboliths,") and in the remains of inflammatory exudates where these have undergone incomplete absorption, for example, in the pleura or pericardium. One of its commonest sites is in old tuberculous lesions, and it may also be found in old infarcts: in the dead and retained fœtus *in utero* ("lithopædion"): in some tumours (*e.g.*, in myomas, as the so-called "womb-stones," and in psammomas): in dead, and even around living, parasites (*e.g.*, in the capsule of *Trichinella spiralis*—p. 417 *et seq.*): and in and around included foreign bodies. Calcification is an important agency in the production of some varieties of calculi, for example, in gland-ducts, or in hollow organs, *e.g.*, in the case of biliary (gall-stones), renal, vesical, intestinal, salivary, and pancreatic calculi. Many calculi start originally as small collections of inspissated mucus, degenerated cells or inflammatory products, these becoming first infiltrated and then surrounded by consecutive layers of lime or other salts. In the same way, urinary or other crystals and foreign bodies may act as "nuclei," around which calculi may be formed by accretion of lime, often mixed or alternating with other substances, *e.g.*, with uric acid, and urates, in the case of urinary calculi (*see* p. 886): or with cholesterol and bile-pigment in the case of gall-stones (*see* pp. 786–790).

Effects of Calcification on the Tissues. Heart-valves, arteries, tendons etc., affected by the change, become more rigid, and may show a loss of elasticity and increased brittleness which may render them liable to rupture. The affected parts become hard, white, whitish-yellow, or slightly brownish, and opaque in appearance; the lesions are often rough and gritty or nodular to the touch. In the case of calcification of old tuberculous areas in the lung, or of old caseous bronchial glands, there is often deeply carbon-pigmented fibrous tissue mingled with or surrounding the calcified areas.

Microscopically, there is seen an aggregation of small refractile granules or larger masses which are stained a bluish-black by hæmatoxylin, a bright pink with alizarin, or black with various silver-impregnation methods.[1]

Mechanism of the Process. The calcium salts found in such calcified areas are derived from the blood. According to Wells,[2] their deposition is a physical rather than a chemical process—the amorphous or hyaline condition of the tissues, probably together with an alteration of carbon-dioxide concentration in them, tending to cause precipitation of the salts in the same proportion as that found in normal bone, viz., $3Ca_3(PO_4)_2 : CaCO_3$. As the situations where calcification takes place are often devoid of cells, these seem to take no part in the process. There is thus a distinct difference between such calcification and normal, or even pathological, ossification.

Calcification is frequently found accompanying and following fatty degeneration, *e.g.*, in atheroma of the aorta; and it has been suggested by Klotz that the sequence of events in calcification is first the formation of fatty acids from the fats, which then combine with sodium and potassium salts in the tissue-fluids to form soluble soaps, and these in turn are replaced by insoluble calcium soaps. Gradually the latter become transformed into calcium carbonate and phosphate as the final products in the calcareous deposit. While this mechanism may operate in the calcareous deposits found in old areas of fat-necrosis, it is doubtful if it is applicable to calcification in general.

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[1] For full details and references to calcium-staining *see* G. R. Cameron, *Jour. Path. and Bact.*, 1930, **33**, 929.

[2] Gideon Wells, *loc. cit.*, p. 495. (*See* footnote, p. 216.)

Other Disturbances of Calcium-Metabolism. Calcium-metabolism may be modified in other ways besides in the production of calcification.

Deficient intake of calcium of itself leads to a condition of osteoporosis, or rarefaction of bone. A low phosphorus-intake may also lead to deficient deposition of calcium in bone.

If vitamin D is deficient, the calcium is not efficiently absorbed or utilised and **rickets** develops (pp. 440 and 1214). If there is both low calcium-intake and vitamin-D deficiency, **tetany** is apt to occur. Tetany is a condition of spasm of the muscles, especially of the limbs, due to the increased nerve-irritability. In the adult, the combined deficiency of calcium and vitamin D causes **osteomalacia** (pp. 440 and 1211). In some forms of gastro-intestinal disease in children in which the primary abnormality appears to be an inability to absorb fat (**cœliac disease**), there may also be defective absorption of calcium with the production of tetany and rarefaction of the skeleton.

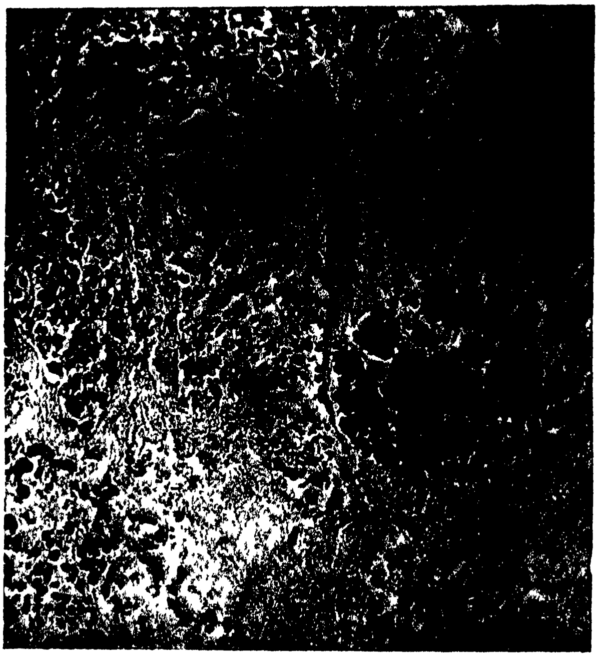

FIG. 112. Area of calcification occurring in a necrotic area in a sarcoma. The calcareous particles are deeply stained with hæmatoxylin. × 200.

Where vitamin D is in excessive amount, and where there is sufficient calcium-intake the blood-calcium rises and there is **deposition of calcium** in abnormal situations such as in the muscle-coat of the arteries, in the heart-muscle, stomach-wall, lungs and kidneys ; in the kidneys the formation of calculi may result (pp. 441 and 886 *et seq.*).

Parathyroid control may be at fault. If there is parathyroid deficiency, from removal or destruction of the glands, the blood-calcium falls to a low level and tetany may develop. This can be prevented by giving parathormone *plus* a high calcium diet. If there is **excess of hormone,** as in the case of certain tumours of the parathyroid, there may be excessive mobilisation of calcium. The bones are depleted and become soft, giving rise to the condition of **osteitis fibrosa** (pp. 838 and 1210–11), the blood-calcium rises, there is excessive excretion by the kidneys and renal calculi may form. Also, as in hypervitaminosis D, there may be deposition of calcium in arteries, etc. This is known as **metastatic calcification.**

Under the terms **calcinosis circumscripta** and **calcinosis universalis** have been described an uncommon disorder of metabolism (Bauer) characterised by the deposit of calcium salts in the subcutaneous tissues, tendons and connective tissue of muscles. The former type occurs particularly in women past middle life, the latter in children.

Errors in Excretion. In certain rare cases, in children or young people, chronic renal disease leads to an excessive use of calcium as a base to neutralise defective excretion of acid-radicles. There is thus a deficiency in the amount of calcium available for the formation of bone, and a condition of rickets, known as **renal rickets,** develops.

In some cases of exophthalmic goitre, there may be also excessive loss of calcium, with rarefaction of bone.

Note.—A fuller account of disorders of calcium-metabolism may be found in "Recent Advances in Pathology," by Hadfield and Garrod, 3rd ed., 1938, Churchill, London.

CHAPTER IX

NECROSIS AND GANGRENE

In studying these subjects, it is important to remember the part played, not only by the active causal agent, but also by the tissue upon which it acts. Both necrosis and gangrene may be brought about in healthy tissues by a powerful physical, chemical, or toxic agent; but they occur more readily in tissues whose resisting power is lowered from any cause. Certain tissues are more resistant than others and causes which give rise to serious destructive changes in the brain or in highly-functioning secreting-cells would have little or no effect on tissues such as skin or connective tissue. In order that a tissue, the cells of which are well nourished and possessed of an average normal functional capacity, may die, the causal agent must be an active one; but, on the other hand, a slight cause, especially if acting for a prolonged period, may bring about extensive destruction in a tissue imperfectly nourished and the resisting power of which is, in consequence, diminished.

NECROSIS

Virchow applied *the term* **necrobiosis** *to the* gradual death of individual *cells or groups of cells in the living body, this* death being the result of retro*grade and degenerative processes; whilst the term* **necrosis** *was applied to* conditions in which the death was more rapid, *and directly followed some* definite cause. The term **necrosis** is now commonly used to indicate the death of cells or tissues from any cause. Such death results in cessation of function, and may be recognised by certain histological and chemical changes which are in reality post-necrotic and consist of the disintegration of the damaged cell or tissue. If death is produced by an agent which also arrests such disintegration or autolysis, there may be little or no histological changes demonstrable. Thus, if fresh tissue be immediately killed by placing it in a solution of corrosive sublimate or other efficient fixative, the histological elements may be preserved with little if any visible alteration. Indeed, most of our conceptions of finer structure formerly depended and to a large extent are still based upon such arrest of disintegration in the killed cell.

Causes of Necrosis :—

1. **Arrest of the Circulation.** For the healthy nutrition, growth and development of any tissue, it is essential that its blood-supply should be satisfactory; and, therefore, any factor which interferes locally with the normal circulation will be a cause of degenerative processes; and, if that factor brings about an absolute arrest of the blood-supply, necrosis may follow. This will certainly be the result if the arrest of the circulation be permanent; but, with even temporary arrest, extensive necrotic changes may

be produced. In rabbits, obstruction of the renal artery for from one-and-a-half to two hours is sufficient to produce necrosis of the greater part of the highly-functioning epithelium of the secreting-tubules, even if the circulation afterwards becomes perfectly re-established. Highly-functioning and delicate tissues suffer more rapidly and severely from alterations in the arterial supply than do the more resistant supporting tissues. Temporary arrest of the circulation may cause extensive necrotic changes in secreting-cells or in the brain-tissue, whereas it would have little or no appreciable effect on the skin or on connective tissue. The degree and extent of the necrotic change depend upon the amount of collateral circulation; the more efficiently and rapidly it can be established, the less the liability to necrosis. But, where such collateral circulation is inadequate, as in areas supplied by the so-called end-arteries (p. 172), *e.g.*, in the spleen or kidney, necrosis follows.

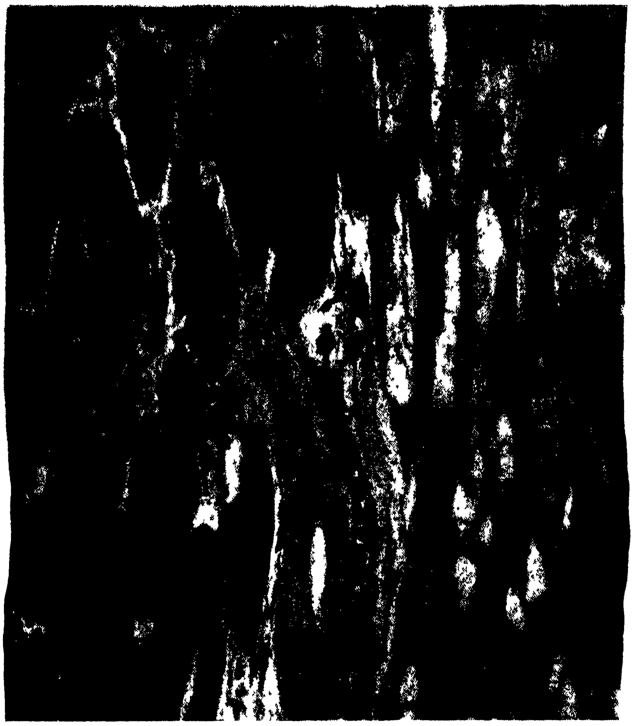

FIG. 113. Necrosis of muscle-fibres of heart resulting from thrombosis in a branch of the coronary artery. The necrotic fibres are pale and show loss of striation and of definite outline. Hæmatoxylin and van Gieson's method. × 300.

The arrest of the circulation may be brought about in various ways, *e.g.*, by thrombosis: embolism: pressure from without by *ligature, tumours, aneurisms,* or inflammatory exudates: or by spasmodic contraction of the vessels, produced by chemical agents or by nervous influences: or by disease of the vessel-wall. Ligation of an artery not only occludes the vessel itself but damages the nerve-elements in its walls, and thus interferes with the establishment of the collateral circulation by producing reflex contraction of the collateral vessels owing to stimulation of the sympathetic nerve-mechanism, an ill-effect which, from an operative point of view, may to a large extent be obviated by (1) resection between two ligatures of the blocked segment of artery: (2) proximal periarterial sympathectomy: and (3) infiltration or section of the appropriate regional sympathetic ganglion or plexus.[1]

Thrombosis. The effects of this are well illustrated in the condition of senile gangrene, where, with a feeble circulation, extensive degeneration and narrowing of the arteries takes place; but similar results may follow thrombosis from other causes.

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[1] "Effects of Arterial Ligature on the Vasomotor System," by R. Leriche and M. G. Werquin, (Strasbourg), *Lancet*, 1940, ii, 296.

Thrombo-angiitis Obliterans (pp. 482-3). In this condition, described in detail by Buerger (1908 and 1929) and sometimes called by his name, there is an inflammatory proliferation in the vessel-wall and thrombosis of the lumen. The ætiology is obscure. It affects males and the Hebrew race is especially prone to it. It occurs in the earlier age-periods (below 30 or 40) and may lead to the production of gangrene with severe pain, usually in the lower limbs. Heavy tobacco-smoking is believed by some to play an important part in its causation.

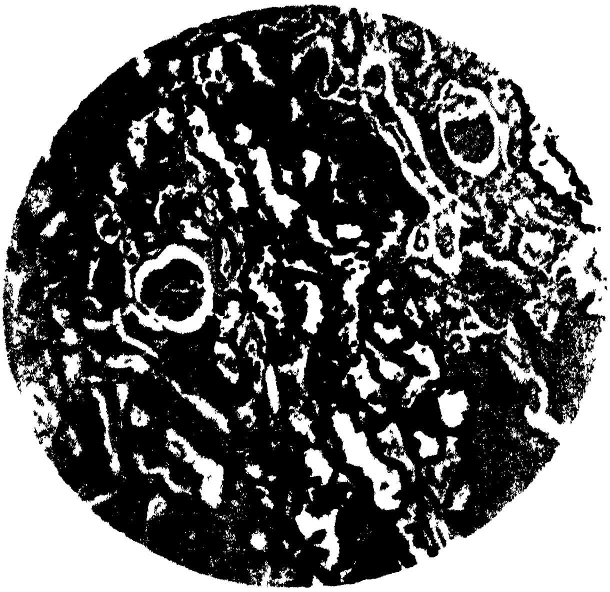

FIG. 114. Kidney, showing calcification in necrotic tubules. From a rat poisoned by corrosive sublimate. The calcium has been stained by alizarin. (By courtesy of Dr. R. F. Ogilvie.) × 100.

Embolism. Necrotic areas, following the impaction of emboli in the corresponding arteries, are seen frequently in the spleen and kidney in cases of cardiac disease, especially when there are loose, easily detached vegetations on the valves, or where there are thrombi in any of the chambers of the heart. A detailed description of this process will be found under Infarction (pp. 172 and 173 *et seq.*).

Spasmodic Contraction of the Arteries. Symmetrical necrosis of the fingers and toes occasionally follows the spasmodic contraction of the arteries in chronic ergot-poisoning and in " Raynaud's disease " (pp. 167, 187, 483, 1184 and 1190 *et seq.*).

2. **Physical and Chemical Agents.** Necrosis may be caused directly by prolonged or excessive pressure, especially if the vitality of the part be lowered. Bed-sores (**decubitus**) in debilitated people or in those suffering from nervous diseases, *e.g.*, acute myelitis or hemiplegia, are the most familiar examples. No doubt, in most of these, lowered vitality and diminished sensation play an important part, but it is certainly the pressure which is the ultimate cause of the necrosis, for it is over the parts that are exposed to its action, *e.g.*, the sacrum, the iliac crests, the trochanters, the internal condyles of the femur, and on the back of the heels, that bed-sores develop ; and, by careful attention to the minimising or prevention of such pressure, the sores may be

avoided. Necrosis of healthy tissues may be produced by severe crushing injuries, but, in the majority of cases of necrosis following pressure, the principal factor is interference with the blood-supply by laceration or thrombosis of the vessels. Much of the necrosis following severe crushing injuries is secondary to damage to the arteries of the part. In the necrosis following tight bandaging or the too prolonged application of a tourniquet, the obstruction of the vascular supply is the principal cause.

Mineral acids, carbolic acid, and other caustics and corrosives act directly upon the tissue-cells, causing their degeneration or death. This is seen, for example, in cases of poisoning from the drinking of these, and it also occurs as a result of inhalation of, or contact with, " mustard-gas " and other kinds of poison-gas. A serious form of chronic ulceration known as " chrome-hole " may affect workers with chromic acid or the bichromates (p. 549). Other substances such as ergot act on the arteries, causing contraction ; and, if this is prolonged, necrosis results.

The **liver** especially is liable to be damaged by various chemical substances, such as the explosive, trinitrotoluene (T.N.T.), the cellulose-solvent tetrachlorethane, arsenical preparations, etc. Such agents may act alone or their effects may be intensified or made possible by various infections. Usually it is the liver-cell proper that is damaged, whilst the bile-duct epithelium escapes. The effects of such lesions are considered in more detail under Diseases of the Liver (pp. 771 and 777).

Temperature. Extremes of heat and cold (pp. 184 and 186) are in themselves directly injurious to cell-life, and may therefore cause necrosis ; but, in the majority of cases, the high or low temperature acts by causing contraction of the arteries, or by injuring the tissues to such a degree that thrombosis takes place, and the necrosis is, in part at all events, a secondary result of the vascular alterations. This is well illustrated in the condition of trench-foot (p. 186).

The length of time of exposure, the intensity of the heat or cold, and the vitality of the tissues, are each important factors in determining the degree and extent of the resulting destructive changes. Moderate degrees of heat or cold, whilst not injuring healthy tissues, may cause necrotic changes in tissues the vitality of which has been lowered. This is seen in the production of bed-sores which follow the application of over-hot bottles (or even at a temperature not dangerous to ordinary healthy persons) to the limbs of patients suffering from myelitis or other diseases of the spinal cord where the nutrition of the skin and other tissues is impaired.

Electricity and Radio-active Substances. These probably act directly upon the tissue-elements. Necrosis of the skin and other tissues is not infrequently seen after undue exposure to Röntgen rays, or after the too prolonged application of the electrode of the galvanic current. Exposure to the action of radioactive substances such as radium may produce a similar result.

3. **Bacteria and Their Products.** These play an important part in the production of necrotic changes. Such destructive action may be due to some **one** particular variety of organism : to a **mixed infection** : or occasionally to the **combined** or **" synergistic " action** of more than one variety of bacteria—as in a rapidly-spreading necrosis which attacks the skin and is liable to become gangrenous (p. 251), caused by an anaerobic non-hæmolytic streptococcus in

association with a staphylococcus, described by Meleney[1] and associated with his name—neither of these organisms alone producing more than a mild non-spreading infection. Sometimes a bacterial toxin is so potent that the cell is killed outright, but in other instances the degenerative and necrotic process is more gradual, so that the tissues affected undergo alterations in their chemical and staining reactions. The area of necrosis may be local and comparatively large, as illustrated in the widespread necrosis of the epithelial cells of the pharynx brought about by the action of the diphtheria bacillus and its toxin ; or the effect of the toxin may be spread throughout the tissues and organs of the body, and especially in the more highly-functioning cells. This is seen in the necrosis of the cells of the secreting-tubules of the kidney or of the liver in many infective diseases. In certain cases, there are multiple areas of necrosis —**focal necrosis**—in various organs. These are best studied in the liver, but they may be found in the kidney and the spleen, and sometimes in supporting tissues. These areas may be visible to the naked eye, or may be only microscopic in size. They are of common occurrence in typhoid fever, but are also found in diphtheria, in streptococcal septicæmia, and probably in most bacterial infections. They may result from the direct action of bacteria, but probably are caused most commonly by soluble toxic substances produced by the bacteria. In many instances, however, the most careful examination fails to demonstrate the presence of any bacteria in these areas.

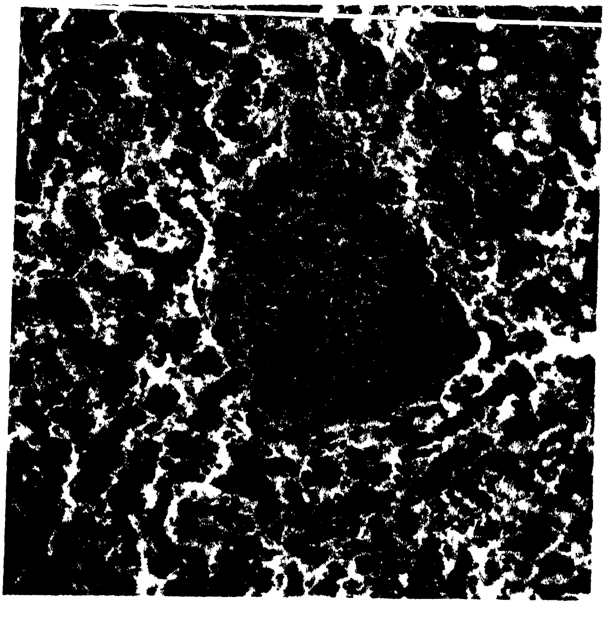

FIG. 115. Liver from a case of typhoid fever, showing an area of focal
Hæmatoxylin and eosin. × 300.

Necrosis, similar to that produced by bacterial toxins, may be brought about by certain vegetable poisons such as ricin and abrin.

Intense Inflammation. In some cases of intense inflammation, the blood-supply to a part may be cut off. The sloughing of large portions of the mucous membrane of the intestine in dysentery is an example of this; and a similar condition is seen in the necrosis of the subjacent bone where the periosteum with its nutrient vessels is separated from the bone by the inflammatory exudate. In these forms of necrosis, there are probably at least two of the causes already enumerated working together, viz., (1) interference with the blood-supply from obstruction of the arteries by thrombosis or some other cause, and (2) the direct action of bacteria and their products upon the tissues.

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[1] F. L. Meleney, in *Surgery, Gynecolgy and Obstetrics*, 1941, **73**, Supplement: *International Abstract of Surgery*, 403, in which are given references to his earlier papers.

4. **Ferments.** **Fat-Necrosis** is found in disease of, or damage to, the **pancreas.** The common antecedent conditions are cholelithiasis and the obstruction of the duodenal ampulla by an impacted stone. At least one pancreatic duct usually opens into the ampulla, and, therefore, bile, bacteria, or cell-debris can sometimes be carried backwards along it into the pancreas, thus activating the pancreatic ferments *in situ*. Fat-necrosis may result also from mechanical injury to the pancreas (p. 792) or from damage to the gland-tissue by infection, especially with abscess-formation : or by tumour-growth. The liberated ferments attack the tissues, the trypsin digesting the proteins, the steapsin splitting the fats. From the necrosis and rupture of blood-vessels there may be extensive hæmorrhage in and around the pancreas—**Hæmorrhagic pancreatitis** (p. 794). From the action of the steapsin there result opaque white patches in the fatty tissue due to the formation of soaps, *e.g.*, in especially the mesentery and omentum. Microscopically the fat-cells are disintegrated and show as granular debris, usually with leucocytic infiltration around. The naked-eye appearances are of diagnostic value, as, when seen on opening the abdomen, they at once direct attention to the pancreas. "**Post-mortem Fat-Necrosis**" is not infrequent from autolysis of the pancreas. In this there are only scattered white spots in and around the pancreas itself, with no hæmorrhage, vascular congestion or leucocytic infiltration, *i.e.*, no evidence of any reaction during life.

Fat-Necrosis of the Breast is uncommon and is due to injury. A mass of necrosed and split fat, in which are cholesterol-crystals or soaps, may be found. It may be mistaken clinically for tumour-growth.

5. **Nerve-Lesions.** Brief reference has already been made to the production of bed-sores by pressure where there is diminished vitality of the part and loss of sensation ; but, in some cases of acute transverse myelitis, the necrosis develops so rapidly that it can hardly be the result of pressure alone, and the disturbance of the trophic and vasomotor innervation must be regarded as its direct and ultimate cause. This condition is known as **acute decubitus.** Section or disease of the peripheral nerves may lead to necrosis. The **perforating ulcer** of the foot in tabes dorsalis is a familiar example, as is also the ulceration of the cornea which follows degenerative changes in the fifth cranial nerve. Anæsthetic leprosy (p. 79) is characterised by extensive necrosis and ulceration, but this cannot be attributed to the nerve-lesion alone. The anæsthesia exposes the parts to all forms of external injury and to secondary bacterial infection, which plays a considerable part in the production of the necrotic process.

Changes which Occur in the Necrosed Tissue. As indicated above, various tissues differ in their susceptibility to necrosis. The most characteristic changes are those occurring in the cell; but, as these are described in Chapter I, (pp. 11 to 14), only brief reference need be made to them here. The chromatin-substance of the nucleus may undergo gradual solution (karyolysis or chromatolysis), and eventually it completely loses its capacity to take nuclear stains. In other, and perhaps the majority of, instances, there is a preliminary fragmentation (karyorrhexis, Fig. 3, p. 14). In this form of cell-disintegration, the chromatin breaks up into a number of irregular granules, which, after the destruction of the cell-body, may become scattered in the necrotic focus, eventually undergoing solution and disappearing. The cytoplasm becomes swollen and homogeneous, and loses its normal reticulated appearance. This is due apparently to an absorption of fluid from the surrounding lymph, the substances absorbed being the coagulable albumins. In some instances, the cytoplasm becomes swollen and vacuolated, and shows a more reticulated structure. One of the commonest changes is a gradual loss of the sharp contour of the cells, and a blending and obliteration of the cell-boundaries (Figs. 115 and 116). The fibrous and muscular tissues, though not so vulnerable as the more highly functioning cells, also undergo necrosis. They become swollen and homogeneous in character, and present the appearance of tissues undergoing hyaline degeneration (Figs. 113 and 117). Striped muscle-fibres lose their striation and become fragmented. Depending to a considerable extent upon the site at which these changes take place, their cause and the condition of the tissues at the time, different appearances are presented. These may be described as :—

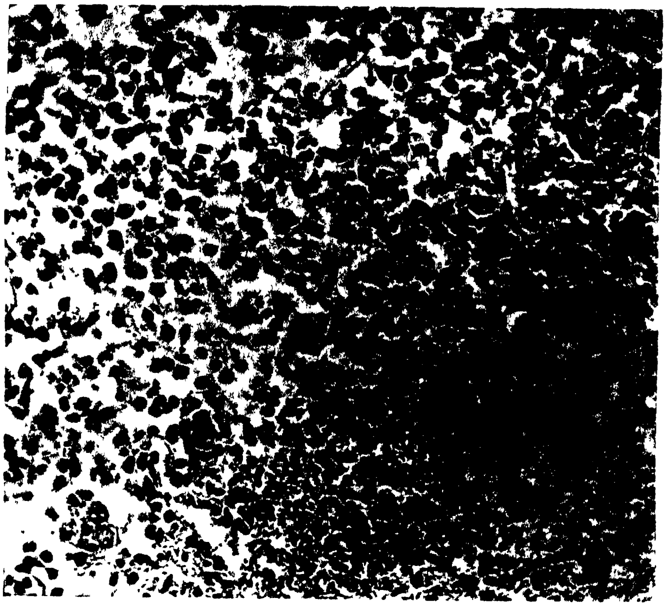

FIG. 116. Area of necrosis in a round-celled sarcoma, showing the fragmentation and disappearance of the nuclear-chromatin, the loss of the cell-outlines, etc. Hæmatoxylin and eosin. × 200.

(1) Coagulation-Necrosis.
(2) Colliquative Necrosis.
(3) Caseation.

Coagulation-Necrosis (pp. 13 and 1242). "Zenker's degeneration" of muscle-fibres is a form of coagulation-necrosis occurring in typhoid fever, but the condition is illustrated more typically by the degeneration which takes place in infarcts in the kidney and spleen. The affected part is usually dry and more or less homogeneous or granular. In naked-eye appearance, it is opaque and of a pale-greyish colour. Microscopically, the outlines of the individual cells or tissues, often mixed with fibrin, may still be recognisable.

Colliquative or Liquefaction-Necrosis. In this form, the necrotic tissue undergoes softening and liquefaction, a process occurring primarily in tissues which are deficient in those coagulable albumins concerned in fibrin-formation. The brain and spinal cord are specially liable to this form of necrosis, infarcts in these tissues undergoing softening, and the dead tissue becoming converted into a soft semi-fluid mass (pp. 1034 and 1039). The colour of this softened area, at first pale, may become red or brown or yellow, from the admixture with pigment from the blood. Secondary softening may occur also in areas of coagulation-necrosis. Polymorphonuclear and other leucocytes may invade the softened area, especially if it becomes infected by micro-organisms, with formation of pus ; but, apart from this, the primary condition is autolytic and non-inflammatory.

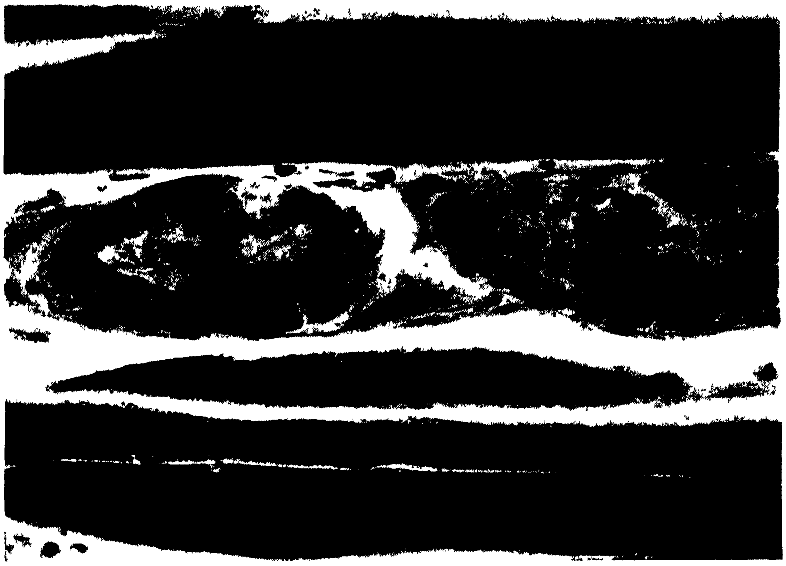

FIG. 117. Zenker's degeneration of muscle (rectus abdominis) in typhoid fever, showing the fragmentation and loss of striation of the degenerated fibres. Hæmatoxylin and van Gieson's method. × 300.

Caseation. Coagulation-necrosis, colliquative necrosis and caseation are *secondary* changes in the dead and degenerated tissue, and are, therefore, strictly speaking, *post*-necrotic. In caseation, the affected tissue becomes dry, and of a greyish-white or pale-yellowish appearance, resembling various forms of cheese. The original structure of the tissue is obscured and lost, cell-outlines cannot be detected, nuclei have lost their capacity for taking up basic stains, and all the affected tissues are converted into an amorphous mass.

Caseation occurs especially in tuberculous areas, and is the classical form of degeneration caused by the tubercle bacillus (*Mycobacterium tuberculosis*) and its products. It occurs also in syphilis, and is common towards the central parts of rapidly-growing tumours. It may supervene also upon coagulation-necrosis.

Sequelæ of the Necrotic Process. If the necrosed area is on the skin or on a mucous surface, it becomes separated from the living tissues, is cast off as a **slough,** and leaves an irregular **ulcerated** area. This is well seen in ulceration of the leg accompanying varicose veins, and also in typhoid and tuberculous ulceration of the intestine. The sloughing is aided by pyogenic organisms which have subsequently gained access to the necrosed part. If the area is in the interior of a solid organ or in a position where separation cannot take place, there follows an attempt at absorption, more or less successful according to the nature and size of the area of necrosis to be removed and which comes to act like a foreign body. Leucocytes, both polymorphonuclear and mononuclear, migrate from the adjacent vessels and invade the dead tissue. Many of them die, and their remains, as well as many still active leucocytes, form a zone round the area of necrosis. Later, these dead leucocytes become absorbed. New vessels, formed by budding from the adjacent vessels, grow into the necrosed area. These are accompanied by connective-tissue and other cells, which arise by proliferation of the endothelial and fixed connective-tissue cells of the part. The necrotic area, if small, may be **absorbed completely** and replaced by fibrous tissue There may be regeneration of even highly functioning and specialised cells, but nerve-cells are not replaced. This regeneration takes place by the multiplication of the surrounding cells. If the affected area is larger, the **absorption is generally incomplete,** a central whitish or yellowish, caseous-looking area, surrounded by a zone of well-formed fibrous tissue, persisting—a condition well illustrated in some infarcts in the spleen and kidney. In these caseous-looking areas, lime-salts may be deposited, or in them may be found fatty acids, cholesterol, blood-pigments and triple phosphates. If the necrosed area becomes infected secondarily by septic organisms, or if pyogenic bacteria are introduced by or along with the causal agent, *e.g.*, by an embolus following the detachment of a portion of a vegetation in ulcerative endocarditis, purulent softening and **abscess-formation** may follow. In some cases where absorption fails, the dead part is cut off completely from the living tissue, and, if the necrosed tissue is specially resistant, it remains

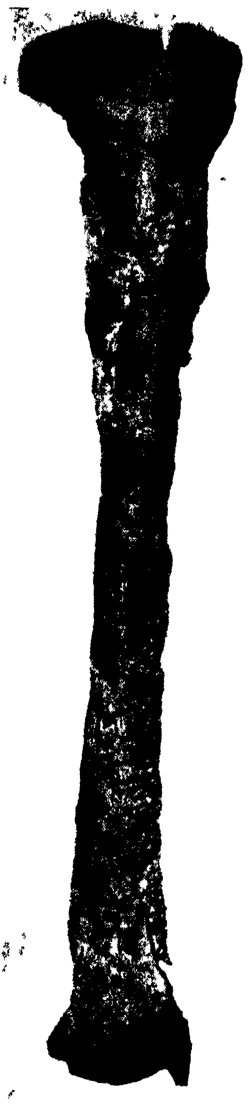

FIG. 118. Tibia of a young person showing necrosis. A dead portion (sequestrum) is visible in the upper half and is partly surrounded by rough new bone (involucrum). The lower end and portions of the upper epiphysis are also necrotic.

for a considerable time practically unaltered in its structure, though around it a pronounced proliferation of the adjacent tissues is observed. A typical example is seen in necrosis of bone, where the separated and dead part or **sequestrum** still retains to a large extent its normal microscopic structure, and is surrounded by a bony capsule—the " new case " or **involucrum**—which is a product of a formative periostitis (Fig. 118).

GANGRENE

Gangrene may be defined as that condition of any of the tissues of the body in which there is **necrosis combined with putrefactive changes.** The tissues often undergo a primary necrotic change (p 245), and the bacteria which cause the putrefaction are introduced, generally from without, into the dead or dying tissue. On the other hand, the infective agent may be the cause both of the necrosis and of the decomposition. In these latter instances—the forms of **primary gangrene**—we have to deal either with specific gangrene-producing bacteria, or with ordinary bacteria acting on devitalised tissues. Most writers have described two forms of gangrene—the " moist " and the " dry " ; and, though this is convenient, and practically essential from the clinical standpoint, the distinction has, we think, led to erroneous statements. Dry gangrene

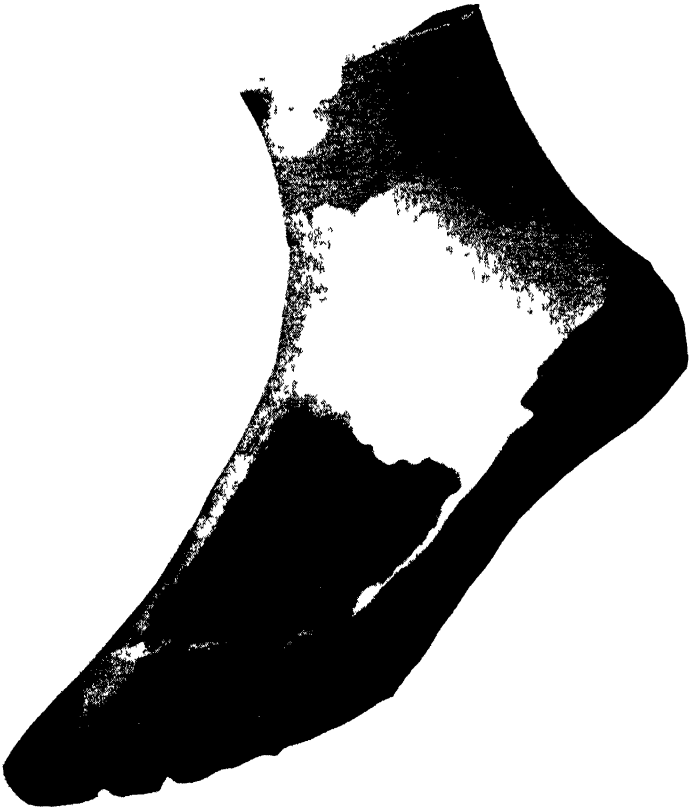

FIG. 119. Dry gangrene of foot. The affected areas are dark in colour and were shrivelled and dry. The anterior and posterior tibial arteries were calcified and thrombosed.

is regarded by many as a form in which bacteria are not present, and which is caused mainly, if not wholly, by arterial obstruction, while the moist form is held to be due to the action of infective agents. The difference between the two is in reality one of degree and of situation rather than of kind. **Bacteria are, in fact, found in both.** If the tissues are devoid of moisture, or are in a situation where evaporation can readily take place, or, in some cases, if the degeneration and death be slowly produced, dry gangrene is the form most likely to occur. **Bacteria are present,** but, in the absence of moisture, are in an unsuitable environment, and do not readily multiply. The classical example is senile gangrene of the foot (Fig. 119), in which the tissues, at first pale from interference with the circulation, become hard and dry, shrivelled, and mummified. The hæmoglobin in the dead part is diffused through it, undergoes decomposition, and stains it a dark-brownish or black colour. If, on the other hand, the tissues contain abundance of moisture, or are in a situation in which evaporation does not readily take place, or if the area be large and the gangrene rapidly produced, the moist form is found ; and, as a natural result of the condition of the tissues, bacteria which were originally present, or which have been subsequently introduced, multiply rapidly and produce secondary changes. If gas-forming organisms are present, the decomposition leads to the production of **gases** of various kinds, which often have a foul odour. These gases, acting on the hæmoglobin or other pigments in the part, produce green or greenish-black discoloration. Poisonous products of various kinds are also formed, and great destruction, with softening and complete disintegration of the tissues, results. The toxic products are absorbed into the general circulation, and give rise to degenerative changes in various organs of the body, or cause the death of the individual. Moist gangrene occurs usually in tissues or organs naturally exposed to infection by saprophytic micro-organisms, *e.g.*, the cutaneous surface generally, lungs, intestine, mouth, and external genitals.

Primary Gangrene. In this form of gangrene, the infective agent is the primary cause both of the destructive and of the putrefactive changes. Certain bacteria, *e.g.*, " *Vibrion septique* " (*Clostridium œdematis-maligni*), *B. welchii* (*Clostridium welchii*) and other allied anaerobic organisms, produce direct death of the tissues, with abundant serous exudation and excessive gas-production. The gas formed is due mainly to the saccharolytic action of the bacteria ; the liquefaction results from their proteolytic properties. The condition may spread very rapidly, and large areas become converted in a few hours into a dark-greenish emphysematous mass, which is infiltrated with blood-stained serous fluid. If the nutrition of the tissues is impaired, this form of gangrene is more liable to occur. **Cancrum oris, gangrenous vulvitis,** and **hospital-gangrene** are due to some of the commoner bacteria acting on devitalised tissues. The first two of these are rapidly-spreading forms of gangrene, which are seen in ill-fed, unhealthy children living under bad hygienic conditions, or in children convalescing from some acute infective fever. The third, which received its name in the days before the introduction of antiseptic and aseptic surgery, is a similar condition which attacks recent or granulating wounds. The tissues at the seat of infection become swollen and inflamed, and in the centre an ash-grey slough appears. This soon separates from the surrounding inflamed tissue, and leaves an irregular, excavated and foul ulcer. The sloughing spreads rapidly; and, if the patient lives long enough, large areas of tissue are completely destroyed, the adjacent parts becoming involved to a greater or less extent.

Gas-Gangrene. During the War of 1914–18 this occurred as a serious complication of wounds. It was " primary " in the sense that the causal organisms were introduced at the time of wounding. Although it might follow upon any form of injury, it was observed especially in (1) deeply-penetrating wounds, with a small point of entrance and widespread destruction of muscles, etc., in the course of the bullet or other missile : and (2) wounds in which, besides the destruction in the line of the missile, there was also a considerable zone of damaged tissue outside the actual track. There seems no doubt that fatigue, and particularly an impoverished blood-supply to the part, however brought about, are potent factors in favouring the development and spread of these gangrenous conditions. These anaerobic bacilli of the saccharolytic group, mentioned in the foregoing paragraph, particularly *Clostridium welchii*, invade the muscles and spread widely along the interstitial tissues. Sometimes a single muscle, or a group of muscles, is attacked ; and, in other cases, the whole of the muscles of a segment of a limb, or even the whole limb, may be involved. Effusion occurs and the sarcolemma-sheath becomes separated from the muscle-fibres by this fluid, which contains the bacterial toxins. As a result of this separation, the muscle-fibres lose their blood-supply and undergo necrosis. The rapid spread of the disease is due in part to this bathing of the tissues in the toxic effusion and the extensive associated necrosis, but chiefly to the invasive power of the organisms themselves in the muscle and other tissues, the constituents of which, including the muscle-sugar, form a suitable " culture-medium " for their growth. The bacteria are present usually in enormous numbers, and their toxins act, not only on the muscles, but also on the nerves, the epidermis, and, later, on the blood-vessels and the connective tissues. Inflammatory reaction is absent in the necrosing muscle-fibres ; but there may be a pronounced leucocyte-infiltration of the subcutaneous and connective tissues. Thrombosis of veins and capillaries is a frequent, but not an invariable, phenomenon. No special changes are seen in the blood-vessels, except, in the later stages, when their walls share in the necrotic processes which are taking place in the surrounding tissues. Œdema and gas-formation are striking features of the condition. The cells of the internal organs, especially of the liver and kidney, show marked cloudy swelling or necrotic changes, and small spaces, due to bubbles of gas, may be seen in these organs. This appearance is seen also in advanced post-mortem putrefaction, producing a very characteristic " rubber-sponge " appearance in the liver (Fig. 111, p. 237) or brain (Fig. 120, p. 254), and, in the subcutaneous and other connective tissues, an appearance simulating surgical emphysema (*see also* Post-mortem Changes, p. 236). It should be noted that the **toxigenicity** and the **invasive powers** of the organisms are *not* always parallel. In actual practice, indeed, it has been found that serum-treatment is sometimes more efficacious against strains of *Cl. welchii* of high toxigenicity than against those *of lower toxin-producing power but of higher invasiveness.*[1] *Later, other organisms of putrefaction, which have been introduced at the time of the infliction of the wound or have subsequently gained entrance, develop, and ordinary mixed gangrene supervenes.*

Gas-gangrene may occur also in civil life, *e.g.*, in motor accidents in which there is often extensive laceration and damage to tissues, and gas-producing organisms are introduced at the time of accident.

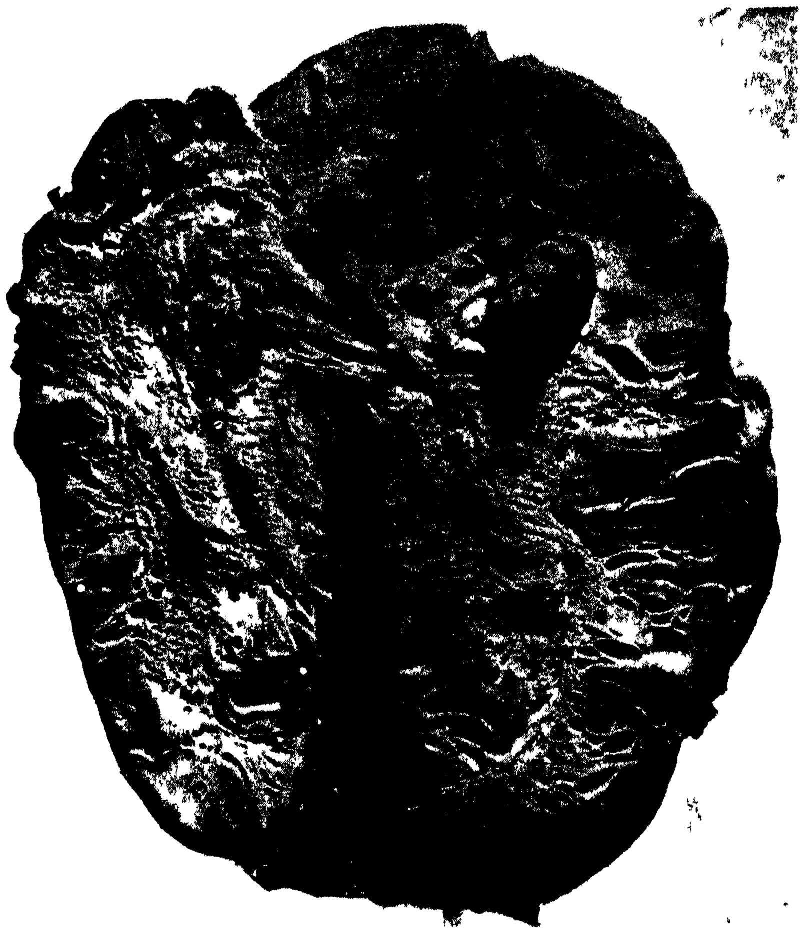

Fig. 120. Brain: gas formation in infection with *Clostridium welchii* following upon craniotomy (in a woman of fifty-eight) for the relief of pressure caused by the metastatic nodule of carcinoma seen in the white matter of the right frontal lobe, and which has been "dissected out" by the gas production around it. Throughout the rest of the brain is seen the characteristic "honeycomb" or "Gruyère cheese" appearance due to the production of innumerable gas cavities, many of which have an elongated or lentiform rather than a spherical, shape because of their lying between and separating the nerve bundles in the white matter. (W. E. H. case.)

In addition to the local lesions of gas-gangrene, profound general toxæmia from the circulation of the toxins of the bacteria in the blood is not uncommon.

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[1] Dora Stephenson and Helen E. Ross (Welcome Research Laboratories), "The Chemotherapy of *Cl. welchii* and *Cl. septique* in Mice," *British Medical Journal*, 1940, i, 471.

Similar toxæmia has been observed in strangulation of the intestine, and the toxin of *Bacillus* (or *Clostridium*) *welchii* has been found in obstructed loops (Williams, 1927). This organism and allied anaerobes are found in the normal intestinal contents and are increased in certain conditions, *e.g.*, in achlorhydria. Anti-serum is used both for prophylaxis and in treatment.

Gangrene is occasionally the sequel of a disease in which the tissues have become devitalised, and in which the circulation is enfeebled in certain acute infective fevers, such as typhoid. The typhoid bacillus may settle down in bone, periosteum, or elsewhere, and necrosis with gangrene may be the result ; but, in these cases, it must be remembered that some trivial injury may have caused certain destructive changes which had preceded the invasion of the bacteria, or that thrombosis has occurred in some of the smaller vessels, with consequent death of some small areas of tissue.

In secondary gangrene, the putrefactive changes are secondary to or consequent upon necrosis. In many cases, a primary obstruction of the arterial supply causes the necrotic change ; and the bacteria which are already present, or which are introduced from without, bring about the gangrenous condition. A characteristic illustration of secondary gangrene is found in strangulation of the intestine, when the arterial supply is obstructed. If the tissues are examined in the early stage, all the changes which have already been described under necrosis are found. Bacteria multiply with rapidity in the dead portion, and these or their products cause alterations in the blood-pigment, and consequent dark staining of the part. In the late stages, sloughing and gas-production (especially if the tissues are infiltrated with fluid) or the dry form of gangrene may occur. In the majority of cases, there is no difficulty in differentiating between the primary and the secondary forms of gangrene, but not infrequently it is almost impossible to make the distinction.

Gangrene of the lung sometimes follows pneumonia. It may, however, appear independently and without previous consolidation, in which case we believe the gangrene to be always directly due to the invasion of dead or dying tissue by putrefactive organisms. In the brain, gangrene is always the result of the introduction of infective organisms, generally from the nose or ear ; or in compound fracture of the skull : or following operative interference, especially if **hernia cerebri** supervenes ; and it is often impossible, in a given case, to say whether it is to be classified as primary or secondary.

The gangrene which sometimes occurs at the free ends of the nose, fingers, or toes must be regarded as almost always secondary. The tissues of the part have undergone degeneration owing to the impairment of the blood-supply, or because some of the vessels have become thrombosed, or because there has been injury to, and consequent destruction of, a tissue which is already very feebly nourished. This degenerated tissue becomes invaded secondarily by bacteria, and, dependent on the conditions present, either the dry or the moist form of gangrene may result.

The gangrene which occurs in patients with diabetes mellitus may, in part, be due to some special factor of which we are at present ignorant, but there seems no reason to doubt that the abnormal metabolism which brings about such wasting of the tissues must, of itself, so weaken the tissue-cells in general as to render them unduly susceptible to destruction by slight mechanical, chemical or other form of injury, and thus allow the occurrence of the necrotic and gangrenous processes. In elderly patients, the associated arteriosclerosis in diabetes is an important factor in causing gangrene, *e.g.*, of the foot or leg.

Results of Gangrene. The gangrenous process may spread and gradually involve a progressively larger area of tissue ; or an inflammatory reaction on the part of the healthy tissue may be set up at its junction with the dead tissue, and thus there may be established a protective barrier of developing or newly-formed granulation-tissue—the so-called line of demarcation. This may, in time, lead to the complete separation of the dead part, *e.g.*, toe, foot or leg.

The spreading or diffuse form of gangrene is of the moist type, and develops rapidly, with gas-containing bullæ at various places, and emits a foul, penetrating odour. An extensive spread of gangrene is also, however, seen not uncommonly in the dry, senile form, and is attributable to the imperfect nutrition and consequent defective metabolism of the parts of the body affected. In fact, it may be taken as a general rule that all necroses which are brought about in an otherwise healthy individual by causes other than infective organisms have a tendency to become circumscribed. The inflammatory zone, or line of demarcation described above, completely shuts off the dead area, which, if small, ultimately undergoes absorption or, especially if more extensive, becomes enclosed in a well-formed fibrous envelope. Even in spreading forms of gangrene, there is an attempt to establish this inflammatory zone, but it is more or less imperfect, and fails to act as a barrier to the rapidly-spreading destructive processes.

Note.—Perhaps of some importance in connection with the subject of necrosis and gangrene and in contrast with the results of the destructive action of cold on the tissues described on p. 186, the work by F. M. Allen of New York (*Amer. Jour. Surgery,* 1941, **52,** 225), quoted in a leading article in the *Lancet* (1941, **ii,** 734), suggests that the **application of cold,** *e.g.*, refrigeration at 5° C., may be used to save badly crushed limbs, and to make the amputation of these or even of limbs undergoing diabetic and other forms of gangrene safer by providing the surgeon with a "bloodless shockless field" of operation (*cf.* p. 186). The essential desideratum in this use of cold appears to be that the part must first be rendered **ischæmic.** "When the circulation in a limb is impaired, survival is aided by cold rather than heat ; for cold, by reducing the metabolism of the tissues, cuts down the oxygen requirements and thus offsets the diminished blood-supply. Moreover, cold arrests the growth of pathogenic organisms and in the ischæmic limb this may make the difference between life and death" (*loc. cit.*, p. 734). We await with interest the confirmation or otherwise of this suggestion that the application of cold is, in these circumstances, not only safe but highly beneficial. As the *Lancet* remarks, Allen "has attempted to test his ideas by experiment and his findings certainly merit further study."

CHAPTER X

ATROPHY

THE expression "**atrophy**" is commonly applied to conditions where there is wasting of the organs and tissues, generally preceded or accompanied by certain retrograde processes in them, and usually characterised by diminution in their size, or even by their complete disappearance. It should be noted, however, that the special functioning-tissue of an organ may undergo extensive atrophy without a corresponding diminution in the actual bulk of the whole organ itself.

The term "atrophy" is sometimes applied to an organ simply because it is smaller than normal, but this may be due to **hypoplasia,** in which, developmentally, proper size has never been attained : to **aplasia,** in which proper form and structural organisation have not been acquired : and to **agenesia,** in which even the **anlage** of the part was lacking and no development at all could occur, and which is therefore in no sense an atrophic change ; or the reduction in size may be caused by an active destruction of the cells of the organ by bacterial or other poisons, *e.g.*, the so-called "acute liver-atrophy" which is essentially necrosis and not atrophy. Many conditions, however, arise in which it is difficult to draw a clear line of demarcation between true atrophy and mere reduction in size and weight brought about by retrogressive changes in the tissues and organs. Thus the atrophic changes which occur with advancing years are due partly to degenerative changes, partly to faulty nutrition and partly to alterations in the functional activities of the endocrine organs. In this chapter we purposely use the term "atrophy" somewhat indefinitely and apply it to conditions in which there is wasting of tissues and organs from various causes.

Although the causes and results of general and of local atrophy are in the main similar, it is convenient to discuss them to a certain extent independently.

General Atrophy. During the period of development and growth of the body, the anabolic or constructive processes are greater than the katabolic or destructive. In the metabolism of adult life, there should be a balance of these two sets of processes, whereby the nutrition of the tissues is maintained *in statu quo*. In old age, there is a natural and progressive diminution in the activity and vitality of the tissues, and a gradual falling-off in their capacity for building up and maintaining themselves—the balance between the anabolic and katabolic processes gradually failing, not so much from an increase of the *latter*, as from the slow and progressive decrease in activity of the *former*, whereby the reparative capacity of the tissues to make good the wastage due to metabolism is diminished or lost. As a result, the condition of **senile atrophy** supervenes. An example of this is seen in the atrophy of the lymphoid and reticulo-endothelial cells, and their replacement by fibrous tissue, in the lymph-nodes and the spleen in old age. The lymph-nodes become small and firm ; the capsule of the spleen becomes wrinkled and the weight of the organ may fall as low as 75 to 60 grammes (2½ to 2 ounces). Atrophic changes are seen also in the bones of the skull, the mandible (Fig. 121, opposite), in both the shaft and the articular ends of the long bones, and in the muscles.

In some instances, what is known as **premature senility,** characterised by the abnormally early appearance of these atrophic and other senile changes, supervenes.[1] In certain individuals this is due to ascertainable causes, such as intemperance, prolonged physical or mental strain, present or previous disease, hypopituitarism (p. 808), etc. ; but, again, its cause may be obscure ; and, indeed, in some individuals and families there appears to be a hereditary predisposition towards its occurrence.

Certain factors, some of which have already been dealt with in the Chapters on the Physiology and Pathology of the Cell, are needful for the maintenance of tissue-nutrition and for preserving the balance of the metabolic processes. Thus the functional activities of the organs and tissues must be neither deficient nor excessive in degree or nature. Nutriment must be sufficient in amount and quality, and there must be no interference with its ingestion, digestion, and absorption. Lymphatics, blood-vessels, and the blood itself must be healthy ; and the innervation and consequent trophic power of the tissues must be efficient. An extreme degree of emaciation or general wasting may follow **starvation** and may be due to actual deprivation of food or of some essential food-elements such as vitamins or inorganic salts ; it results from inability to swallow, *e.g.*, in stricture of the œsophagus, or obstruction at the cardiac orifice of the stomach ; or it may be produced by inability to digest and assimilate the food which has been ingested, *e.g.*, in cases of gastric ulcer or carcinoma. Stricture of the pylorus, tuberculous disease of the intestines, lacteals, or mesenteric lymph-nodes, preventing intestinal absorption, may also bring about much the same results. In cases of death due to starvation, in addition to the general emaciation, there is also a profound degree of wasting in the walls of the stomach and intestines, owing to the cessation of their normal functional activities.

General loss of weight, and sometimes reduction in the size of organs, occur in long-continued fevers, tuberculosis, syphilis, some forms of nephritis, diabetes mellitus, certain parasitic infestations, advanced malignant disease and diseases in which there is severe or long-continued diarrhœa, as in cholera or dysentery.

Several causes may be at work in individual instances, and it is often difficult to evaluate the extent of the action of any one of these. The absorption of toxins or of metabolic poisons produces impairment of function and vitality of the organs and tissues, fever and tissue-waste. By impairment of the digestive and other functions, the assimilation of sufficient nourishment is prevented. There is a lack, not only of absorptive power, but an actual loss, frequently over prolonged periods, of substances necessary for the proper nutrition of the body—proteins, carbohydrates and water.

The metabolic poisons generated in the course of some of these disorders interfere with the regulating-centres in the nervous system and cause disturbance of their trophic and vaso-motor functions, leading to the production of vascular and secondary degenerative changes in the tissues. In certain cases, there may be associated endocrine disturbance, with arrest of development or imperfect growth ; and the resulting atrophy may be a pronounced feature. This form of " atrophy " is seen, for example, in the structures of the skin in myxœdema (p. 835) and in the sex-organs in hypopituitarism (p. 808).

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[1] For the cerebral changes in presenile dementia *see* p. 1079 *et seq.*

To a group of cases of general atrophy and emaciation, which are not due to specific fevers, tuberculosis, or other obvious cause, the term **marasmus** or wasting is sometimes applied. Such cases are of frequent occurrence in infancy, and are probably often due to the absorption of toxic substances generated in the alimentary canal, to vitamin-deficiencies, or to simple failure of the normal mechanism of the digestion and absorption of food.

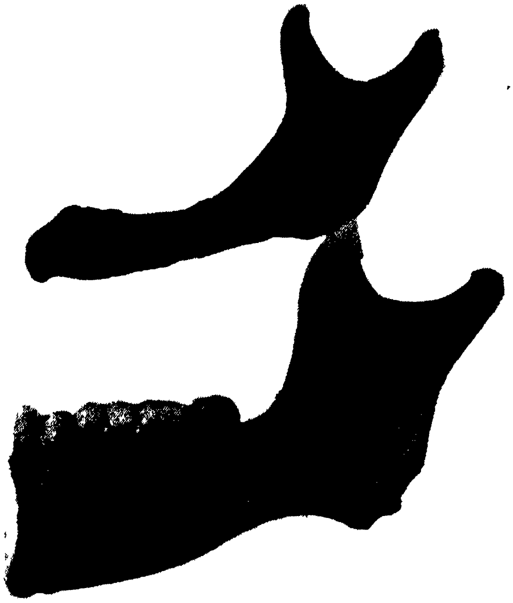

Fig. 121. Atrophy of the lower jaw in old age. The bone is reduced in size, edentulous and with its alveolar border completely absorbed. The lower specimen is a well-developed normal adult jaw for comparison.

Local Atrophy. This may affect an individual organ or tissue in whole or in part, or a group of similar or allied tissues.

Local atrophy may be exemplified in the physiological involution of certain organs and tissues, familiar instances of which take place at all periods of life, for example the disappearance, during intra-uterine development, of the yolk-sac and vitelline duct, the left superior vena cava, the thyro-glossal duct, and many other structures : the involution of the thymus gland during childhood and adolescence, and of the uterus after parturition : the atrophy of the female generative organs at the menopause : senile involution of many organs and tissues, *e.g.*, of certain parts of the osseous skeleton, such as the neck of the femur and the lower jaw (Fig. 121).

Local atrophy in disease is also common, and may arise from various causes, many of which are essentially similar to those which bring about some of the degenerations discussed in the preceding chapters; or which, if more severe, may result in necrosis. Atrophy of the convolutions of the brain occurs in old people (p. 1022), in general paresis and in arterial degeneration.

Defective nutriment, or the prevention of its free access to the part, especially if such obstruction be produced gradually, *e.g.*, by disease of the arteries, is a common cause of local atrophy. Narrowing of the coronary vessels of the heart may lead to extensive degeneration and atrophy of the myocardium. Thickening of the walls and diminution in the lumen of the renal vessels, or obstruction to the blood-flow through the glomeruli, may produce extensive atrophic changes in the various structures of the kidney. The atrophy of the central zone of cells in the lobules of the liver in chronic venous congestion may be due partly to pressure from the distended venous capillaries, but is a result mainly of impaired nutrition and anoxæmia (p. 157), following the stasis of the venous blood.

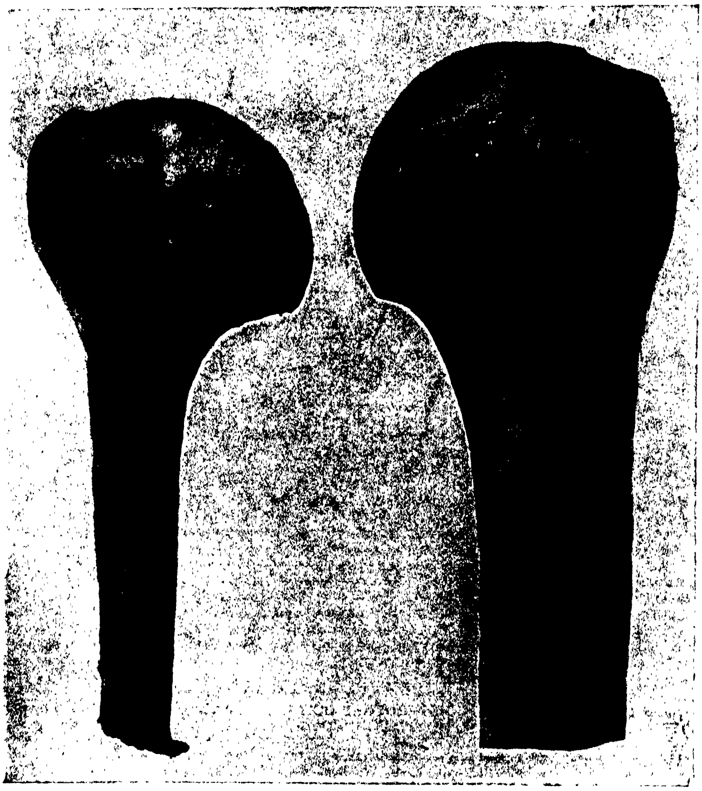
A. B.

Fig. 122. A, atrophy of humerus, especially neck and shaft, following upon amputation: B, head of opposite bone for comparison. (Specimens kindly lent by Mr. Henry Wade.)

As already stated, the tissues, in order to maintain a healthy state of nutrition, must possess sufficient **capacity for assimilation**; and this is impaired in many ways—for example, by various diseases, old age, nervous derangement, abnormal temperature, pressure, etc.

The amount of blood supplied to a given part is governed largely by the degree of functional activity, and therefore **diminution** or **arrest of function** necessarily leads to a corresponding diminution or arrest of the blood-supply. Bones and muscles and muscular organs waste from disuse. The left ventricle becomes considerably atrophied in mitral stenosis, where only a small and feeble stream of blood is projected into it from the auricle (atrium), and, in consequence, it has less work to do in expelling its diminished contents. Similarly, the stomach becomes atrophied if there is chronic œsophageal obstruction ; and the intestine becomes thinned and wasted below a malignant or tuberculous stricture. The muscles in the neighbourhood of an ankylosed joint undergo atrophy from disuse ; and the same condition supervenes in muscles, bone, arteries and other tissues in the stump of an amputated limb (Fig. 122), and in arteries supplying glandular structures which are undergoing or have undergone involution. In the animal kingdom, interesting examples of the atrophy of an organ from disuse are to be found in the almost complete disappearance of the organs of sight in fishes and other animals living in the darkness of the Mammoth Cave of Kentucky, or at great depths in the sea where little light penetrates ; whilst many parasitic animals have come to depend so entirely upon their hosts for nutriment that they have lost almost all specialised organs except those of absorption and reproduction.

Excessive use, especially if of prolonged duration, may also ultimately lead to atrophy, for example in the case of muscles, or even of glandular organs. Thus, in the expanded, immobile chest produced by emphysema, breathing has to be carried on by means of the extraordinary muscles of respiration. These, more especially the sterno-mastoids and scaleni, may at first become considerably hypertrophied ; but, as time elapses, the additional strain upon the activity and nutritive capacity of the muscles cannot be maintained, and atrophy supervenes. A similar condition of atrophy, usually accompanied by degenerative changes and dilatation, may be seen in the myocardium of heart-chambers which have been previously hypertrophied (p. 464).

Disease or injury of the central nervous system or **of the peripheral nerves** may lead to local atrophy of tissues thus deprived of their normal neurotrophic influence. The wasting may be of the muscle as a whole, or individual fibres only may be involved. Special muscle-groups are affected in different cases, according to the site of the lesion ; and the extent and degree of the wasting are also partly dependent on the same factor. Reference has already been made to this when dealing with general atrophy. The change is produced partly by the diminution or cessation of function in the part, partly by changes in the vascular supply, and partly by the loss of trophic nerve-energy. Thus, in infantile paralysis (poliomyelitis anterior acuta, p. 105), and in progressive muscular atrophy (poliomyelitis anterior chronica, p. 1170 *et seq.*), where the motor cells of the ventral horns in certain parts of the spinal cord are destroyed by disease, the corresponding muscles gradually waste. In the former of these diseases, occurring as it most frequently does early in life, not only the muscles, but also the bones, *e.g.*, of the lower limb or of the shoulder-girdle and upper extremity, are often considerably diminished in size, due partly, no doubt, to an arrested development from lack of use, but also largely to their being deprived of the trophic influence of the nervous system necessary to growth and development. Peroneal atrophy (Figs. 754–5, pp. 1173–4) may also be cited as an example of the atrophy of a segmental group of muscles following upon lesions in the corresponding motor nerve-cells in the ventral horns of the spinal cord. In disease of the upper neurones, the wasting is usually less rapid and less extreme than when the lower neurones are involved. Disease or injury of peripheral nerves may lead to wasting of the tissues, and particularly of the muscles, in their areas of distribution. This is seen, for example, in the condition of polyneuritis or "peripheral neuritis" due to alcohol, lead-poisoning, and diabetes (pp. 1184–6). In leprosy, the bacillus may attack and destroy nerve-trunks, with the result that, in addition to the production of wasting of the skin and other tissues, the bones—for example of the hand, especially the phalanges—may become extremely thin and small. In tabes dorsalis or locomotor ataxia (p. 1016), a syphilitic disorder characterised by degeneration and sclerosis of the root-ganglia and dorsal columns of the spinal cord, there may be extensive nutritive changes in the bones and joints.

Influence of Pressure. It was pointed out long ago by John Hunter that continuous pressure causes atrophy, whereas intermittent pressure tends to produce hypertrophy. Continuous pressure causes gradual atrophy from interference with the function and vitality of the tissue itself, and more especially of its cellular elements, cell-division and function being diminished or arrested ; it also acts in part by interfering with the local blood-supply from compression of the vessels and lymphatics. Such pressure-atrophy may occur even in bone, and the sternum or vertebral bodies may undergo extensive erosion in cases of pressure upon them by aneurysms or tumours (Fig. 289, p. 497). The absorption in such cases seems to be to a large extent carried out by means of multinucleated and other phagocytic cells which appear at the surface of the bone in the neighbourhood of such an aneurysm or tumour. Abnormal and long-continued increase of pressure within an organ may similarly lead to atrophy and distension of its component tissues—for example, in the case of the lungs, where prolonged coughing and other causes may produce pressure-atrophy of the alveolar walls and capillaries, as is seen in the condition known as emphysema (p. 524).

Changes Occurring in Atrophying Organs. As a general rule, the more highly endowed and specialised cells are first affected, and exhibit retrograde or degenerative changes, such as the accumulation of a brownish (lipoidal) pigment. The cells themselves may diminish in size and lose their more specific characters, and there is usually a diminution or loss of the power of cell-division and reproduction, and hence a defective formation of new cells to take the place of those which are degenerated and atrophied. The more highly specialised cells may show a degradation in type, or there may even be a degradation in the type of the entire tissue ; for example, connective tissue may be replaced by fatty or mucinoid ("myxomatous") tissue, or cartilage may be transformed into mucinoid tissue. Active phagocytosis sometimes plays a part in these retrograde processes. The supporting connective-tissue framework of the tissue or organ usually exhibits proliferative changes and becomes more completely fibrous, producing the condition known as **atrophic fibrosis,** which may be found as a senile, a degenerative, or a chronic toxic irritative, process. Many of the blood-vessels of the affected area become thickened and narrowed, or even completely obliterated, and may ultimately disappear; although, where there is much increase of connective tissue, re-vascularisation takes place by the proliferation of pre-existing vessels.

From the foregoing it will be noted that, as seen microscopically, atrophy may be **quantitative,** in which the part is smaller because of diminution in the size of cells or other histological units ; or **numerical,** in which there is a reduction in the number of the units. Also, atrophy may be **simple** ; *i.e.*, unaccompanied by other retrogressive changes ; or it may be **degenerative,** in which case it may be designated as **pigmentary, mucinoid, fatty** or **fibrous** atrophy, as the observed alterations require.

The term **metaplasia** was introduced by Virchow to denote the transformation of one tissue-type into another. He originally applied the term to changes between members of the connective-tissue group only, but it is now also used to denote a similar change from one to another epithelial type, *e.g.*, from a higher to a lower, as may frequently be observed in glandular and other epithelial tumours, or in chronic inflammation of a bronchus, where the ciliated epithelium may become changed into one of cubical or flattened, or even into stratified squamous, type. Metaplasia may result from impairment of nutrition and function, but it takes place also during the process of repair and from the demand of the tissues for an altered functional activity. Thus, active blood-forming bone-marrow may be substituted for the more inert fatty marrow, when such a change is demanded by the needs of the organism ; or cartilage may appear in the fibrous tissue of a false joint. Metaplastic changes serving no useful purpose are of common occurrence in neoplasms (p. 275).

CHAPTER XI

HYPERTROPHY AND HYPERPLASIA

VIRCHOW defined **hypertrophy** as **an increase in the actual size** of the individual tissue-elements : and **hyperplasia** as an **increase in their number** ; but there is no general agreement among pathologists as to this precise and limited application of the terms ; nor, indeed, is it practicable to limit our conceptions of the two processes according to these exact definitions, for, in many individual examples of excessive growth, there is, in fact, an increase *both* in the *size* and in the *number* of the essential component tissue-elements concerned. It is, however, convenient to reserve the term "**hypertrophy**" for that condition in which there is a disproportionate increase of an organ or tissue, or of some of its essential component elements, to meet a demand for **increased functional activity,** whether that demand is the result of physiological or of abnormal requirements ; whilst the term "**hyperplasia,**" on the other hand, should be used to denote proliferative changes—not being those of the nature of actual tumour-growth—where **no useful purpose is served** by such proliferation. It is, however, not difficult to cite individual instances of tissue-changes which might be regarded as coming into *both* categories, and we may, therefore, regard these definitions as convenient but not mutually exclusive.

HYPERTROPHY

We may, therefore, define **hypertrophy** as the increase or enlargement of an organ or tissue, in whole or in part, to meet increased functional requirements, whether these are the results of physiological or of abnormal conditions or stimuli, or of a combination of these.

Mere developmental abnormalities and all forms of new growth or neoplasm must be distinguished from conditions of hypertrophy ; whilst abnormal enlargement of organs or tissues due directly to pathological processes (thickening of tissues in syphilis or tuberculosis or changes in bone in osteitis deformans or acromegaly, for instance) must also be excluded as not coming within the category of true hypertrophy.

The commonest examples of hypertrophy to meet abnormal functional demands are to be found in the case of the hollow muscular organs, *e.g.*, the heart, bladder, muscular wall of the stomach and intestine, etc. In these viscera, the condition occurs—usually combined with a varying degree of dilatation—in order to overcome increased resistance to the passage or expulsion of their contents. Familiar instances of such a condition are the hypertrophy of the muscle of the left ventricle where there is increased peripheral resistance

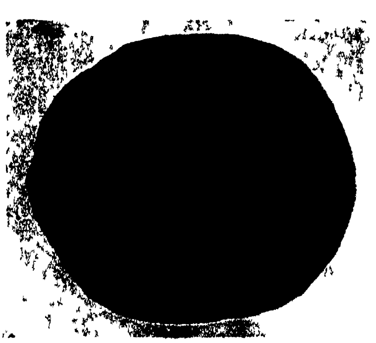

FIG. 123. "*Concentric hypertrophy*" *of left ventricle* in chronic renal disease, seen in a transverse section through ventricles near apex.

to the passage of the blood-stream, *e.g.*, from prolonged spasm of the minute arterioles, from arteriosclerosis, or from narrowing of the aortic orifice: hypertrophy of the muscular walls of the alimentary canal above an obstructive narrowing in any part of its course: or hypertrophy of the bladder above a urethral stricture. As a general rule, the better the general and local nutrition and the more gradual the production of the obstructive lesion, the greater the degree of hypertrophy attainable, and usually also the less marked the dilatation—and *vice versâ*—although, in some instances, there may be a pronounced degree of both conditions, *e.g.*, in the left ventricle in some cases of aortic disease, especially in slowly-produced aortic regurgitation.

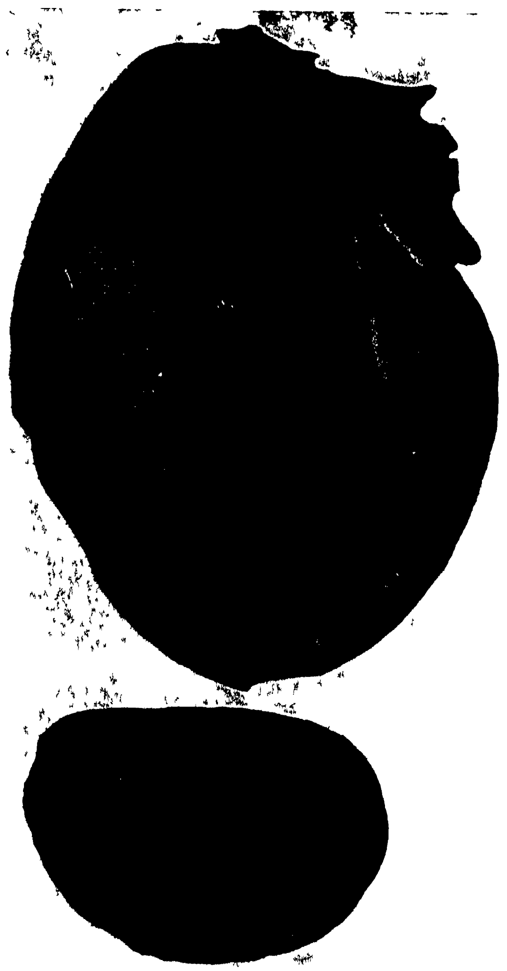

Fig. 124. *Hypertrophy and dilatation of left ventricle* in aortic disease. Below is a transverse section (near the apex of the ventricles) of a similar specimen.

Examples of physiological hypertrophy for the performance of increased function are seen in the enlargement of the uterus during gestation and of the mammary glands during lactation; and an analogous enlargement of these organs may occur under certain abnormal circumstances, *e.g.*, in some varieties of ovarian and uterine disease, with disturbance of the various hormones concerned (p. 916 *et seq.*).

Hypotheses as to the Mechanism of Production of Hypertrophy. In any given case it is likely that several factors have been at work. Some of these are:—

1. **Nervous Stimulation.** The neurotrophic influence of the nervous system upon the tissues has been mentioned in an earlier chapter. It has been thought by some that the enlargement of the uterus in extra-uterine or ectopic gestation might be explained by the influence of reflex nervous action, but it is probable that it is due, in whole or in part, to the influence of the sexual and other hormones (*see* p. 267, section 5). In megalocolon or Hirschsprung's disease (p. 734), the hypertrophy of the wall of the bowel is due to great thickening of the circular muscular coat following a condition of chronic achalasia[1] of

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[1] *Achalasia*, failure to relax, from Greek ἀ-privative and χαλάω, *chalaō*, to slacken or relax, *e.g.*, a bow-string.

the circular muscle in the upper part of the rectum. Dilatation of the colon follows. The achalasia which is thought to be the important factor in the production of this condition probably has a neurogenic basis—hyper-activity of the sympathetic supply to the circular muscle in the upper part of the rectum.

2. **Inco-ordination of Muscular Effort,** *e.g.*, of sphincters, may play some part in the production of hypertrophy of certain organs or portions of organs, and congenital hypertrophic pyloric stenosis may possibly originate in this way.

3. **The Effect of Local Stimulation.** In the case of the connective tissues generally, each is specially adapted to the particular functional strain which it has to bear. The bones, for example, show specially developed thickenings and ridges at many of the points to which muscles are attached. These are more marked in muscular individuals ; whilst, in cases of paralysis, where the muscles cease to act, these muscular ridges and prominences tend to diminish in size or even to disappear.

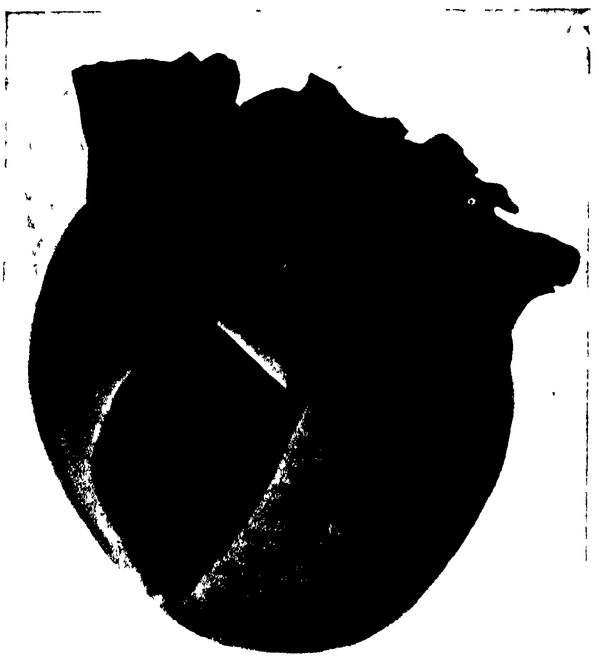

FIG. 125. *Great hypertrophy* (combined with dilatation) of *right ventricle* in mitral stenosis. Note the comparatively small size of the left ventricle.

4. **Excess or Abnormal Character of Nutriment, etc.** A sufficient supply of nutriment, including vitamins, oxygen, and the necessary salts, is essential to the production of hypertrophy, but these factors cannot of themselves bring about the condition. John Hunter's famous experiment of the transplantation of the spur of a cock to its comb led to an extraordinary growth of the transplanted structure, a circumstance probably accounted for, firstly, by the changes in its nutrient supply, the comb being a highly vascular structure : and secondly, by the fact that the spur in its new position was not worn away by friction, as it would have been in its normal position.

5. **The Influence of Hormones or Internal Secretions.** The internal secretion of the pituitary is known to control growth and must therefore influence conditions of hypertrophy. Thyroid secretion has considerable influence on the nutritive capacity of the tissues and on metabolism in general and is similarly likely to be concerned in the production of hypertrophy. The sexual hormones play a most important *rôle* in conditions of hypertrophy and hyperplasia, and some of these changes are dealt with in the chapter devoted to the endocrine system (p. 806).. The influence of the internal secretion of the corpus luteum upon the hypertrophy of the uterine mucous membrane during pregnancy is now well recognised.

6. "**Compensatory Hypertrophy,**" *i.e.*, one organ or tissue taking on the work of another, or one part of an organ taking on the work of the whole, is of comparatively frequent occurrence, and is due to increased functional demands being made upon the surviving organ or part of an organ. If one of two paired organs, for example the kidney, becomes diseased or injured, or is removed, the other may possibly enlarge and take on increased function ; or one set of muscles may take on the function of another weakened or paralysed set, *e.g.*, the extraordinary muscles of respiration may come into play when the action of the intercostals or of the diaphragm is impaired ; or the muscles of one limb may become greatly hypertrophied when the opposite limb is amputated or thrown out of action by accident or disease.

7. "**Complementary Hypertrophy**" is a better term for certain conditions which are sometimes described as instances of "compensatory hypertrophy"; for example, when one lung or part of a lung becomes expanded to fill up the increased space produced by the collapse or destruction of the other, or of another part of the same, lung. This is not wholly a genuine hypertrophy for the purpose of increased function only—the expanded lung being often extensively emphysematous and its functional capacity and efficiency decreased rather than increased—but is largely a physical expansion complementary to the collapse of another part of the contents of the thoracic cavity.

Results of Hypertrophy. Hypertrophic changes may enable an organ to carry on its functions in such a way that the effects of the disease are "compensated for" or neutralised. As an example of this, hypertrophy of the cardiac muscle in valvular and pulmonary lesions, or in arterial disease, may enable the heart successfully to carry on the circulation in spite of increased difficulties. In such circumstances, however, the increasing strain thrown on the hypertrophied tissue calls for ever-increasing nutrition, and, should this prove impossible of maintenance, a process of degeneration supervenes in the hypertrophied and overworked tissue, leading, in the case of the heart, to dilatation and "failure of compensation," or even to the cessation of its function and death. Again, in respiratory obstruction, the excessive strain put upon the hypertrophied sternomastoids, scaleni, and other extraordinary muscles of respiration, may ultimately lead to their atrophy. The over-use of special sets of muscles in certain occupations and sports, *e.g.*, in writers, blacksmiths, cyclists, and others may lead to a similar atrophy following upon hypertrophy, though it is probable that fatigue and degeneration of the associated nerve-cells and nerve-fibres play some part in the process, as well as the over-use of the muscles themselves.

The microscopical changes occurring in the various individual tissues in hypertrophy require only brief reference. It is sufficient to say that, in **true** hypertrophy, there should be little or no structural deviation from the normal. The special functional elements of the tissue may become increased in size, *e.g.*, in the case of the muscular fibres of the hypertrophied uterus. Or, again, there may be a disproportionate increase in one particular histological element of a compound tissue. Microscopical examination of the tissues of hypertrophied organs often reveals the presence of various concomitant degenerative changes. These may be due to other antecedent, accompanying, or subsequent and supervening, morbid processes, and are not to be regarded as characteristic of the hypertrophy itself.

HYPERPLASIA

This term should be confined to conditions in which there is a proliferative change in an organ or tissue of a nature differing from that of the apparently purposeless and often deleterious neoplasm or tumour-growth. Hyperplasia is seen frequently in repair, in cases where the reparative processes have been carried out in excess of the actual requirements. Thus, in repair of a fractured bone, the scaffolding of imperfectly-formed osseous tissue or callus, which acts as a temporary scaffolding for union and support, may be formed in considerable excess; and, if this over-abundant tissue persists, instead of undergoing absorption as it should normally do, the condition may be regarded as one of hyperplasia (p. 1207). Similarly, such hyperplastic phenomena may be seen in the repair of connective tissue, squamous and other forms of epithelium, and more particularly in the excessive proliferative process supervening especially in scar-tissue and known as **cheloid**[1] (pp. 54, 185, 269 opposite, and 301).

Hyperplasia is often the result of irritation, as is well seen in the case of lymphoid tissue following local irritation, or in the reticulo-endothelial system, as in the swollen Peyer's patches of typhoid fever.

Many conditions, some of them previously regarded or suspected as being of neoplastic type, are now recognised as examples of hyperplasia. Certain of these appear to be related to changes in the **endocrine** system, particularly that part of it concerned with the production of **sexual hormones**. Hyperplastic change in the uterine mucosa is an undoubted example of this condition, whilst "enlargement of the prostate" (to be regarded as a hyperplasia and *not* as a condition of "hypertrophy") and alterations in the characters of breast-epithelium are probably often of similar origin.

Finally, though hypertrophy and hyperplasia are distinct and distinctive processes, they may, as already indicated, sometimes occur together, whilst it is possible also to find hypertrophy taking place in hyperplastic cells or tissues and *vice versâ*.

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[1] As this word "*cheloid*" is derived from the Greek χηλή, *chēlē*, a hoof, talon or claw, it should be spelt thus: and *not* "*keloid*," as κήλη, *kēlē*, means a tumour-like swelling, especially a hernia. Cheloid is so called because it spreads into the neighbouring tissues like the claws of a crab, *cf.* Latin "*cancer*," whence, with the same idea, the word "cancer." (*See also* p. 301.)

CHAPTER XII

NEOPLASMS, TUMOURS, OR NEW GROWTHS

GENERAL CONSIDERATIONS

In the whole realm of pathology, and in spite of the vast amount of "cancer-research," there is practically no subject presenting for solution more obscure and difficult problems than the question of the ætiology and ultimate nature of new growths; and, until we obtain more accurate information as to the causation of tumours, any attempt at a general definition of their nature can be regarded as only temporary and provisional. With this reservation, therefore, a neoplasm or tumour may be defined as a new growth arising from pre-existing tissue, independent of the needs of the organism, and subserving no useful purpose, but, on the contrary, often acting deleteriously. It is autonomous, *i.e.*, it follows its own laws of growth, and is not regulated by those governing the tissues of the body in which it is growing. As distinguished from hypertrophy, it is usually devoid of function, but may occasionally possess very imperfect, usually aberrant, and even dangerous and excessive, functional activities. In exceptional instances, the secretion of thyroid, suprarenal and other glandular tumours, either primary or secondary, may serve to replace the normal secretions when these organs themselves are excised or destroyed. There is practically always deviation from the normal structure of the original tissue, and, though nerves have sometimes been demonstrated in tumour-tissue, true nerve-control is probably absent. Further, the life-history —if one may be permitted to use the term when speaking of a neoplasm, "simple" as well as "malignant"—appears to have no typical termination, the tumour-cells seeming to be endowed with the power of continuous, aimless, and unlimited proliferation. In some respects, the vitality of tumour-cells is greater than that of normal tissues, the former being able to grow and flourish at the expense of the latter, which they may destroy and replace. In a patient whose body-tissues are wasting, a tumour may be able to obtain the necessary nourishment and grow rapidly; but, on the other hand, some tumour-cells are more sensitive to the action of radiotherapy than are normal cells.

A tumour is not formed for purposes of repair (although, in some instances, it may supervene in, or be implanted upon, tissues undergoing, or which have undergone, reparative processes); nor is it, unless possibly in the instance of some apparently "virus-produced" growths, the direct result of continued irritation or stimulation by any known bacterial or other organism. It is sometimes an extremely difficult task to differentiate true tumour-growths from certain of the lesions produced by bacterial and other parasitic diseases: from the osteophytic overgrowths of bone in connection with the attachments of muscles: from cheloid[1] of the skin following upon burns, etc.: as well as from the appearances sometimes found as the result of excessive overgrowth or hyperplasia in repair.

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[1] *See* footnote on p. 268 opposite.

All tumours arise by the proliferation of pre-existing tissues—possibly, in some examples, even from a single cell. These pre-existing tissues may be fully developed, they may be actively growing, or may be still "fœtal" or even "embryonic" (*e.g.*, in the case of included "germ-cells," *fœtus in fœtu*, true dermoids, etc.); and they do not, under ordinary circumstances, seem to be the product of something introduced or transferred from without, although, in certain exceptional instances, the transplanation of what appear to be true tumours has been successfully carried out between animals of the same or closely allied species—for example, in certain epithelioma-like tumours in the mouse, and also in the case of an adeno-carcinoma in the same animal. Further reference to these experiments will be made later, and it is sufficient at this point to mention that the cells of the experimental new growths propagated by such implantation are in all probability the "lineal descendants" of the tumour-cells originally introduced.

Recent work in experimental embryology by Waddington, Needham and others appears to offer an explanation of certain difficult problems concerning tumour-formation, especially as regards multiple-tumour syndromes (p. 1130) and the group of teratomatous tumours (p. 351). An account of this important advance in our knowledge is given on p. 291, in the section on Experimental Cancer-Research.

MORPHOLOGY AND HISTOLOGICAL CHARACTERS OF TUMOURS. As already pointed out, all tumours arise from and by the proliferation of pre-existing tissues, but may show great diversity and variation from the original type of tissue from which they grow or into which they should develop; for example, they may tend to become more cellular, and in some cases more, and in others less, vascular, than the original tissue; or, again, in tumours growing from an acinar gland, the tumour-cells may become arranged in gland-like spaces, as in adenomas and adeno-carcinomas, or in solid masses, as in scirrhous and encephaloid cancers (Fig. 172, p. 340).

Other deviations from the original tissue-type may be found: for example, overgrowth of one special tissue-element, as is seen in the proliferation of the fibrous tissue in fibromas, fibro-adenomas and scirrhous cancers: or transitions from one type of tissue to another within an allied group (metaplasias), as is common among the various forms of connective tissue—for instance, between fibrous tissue, cartilage, bone, "myxomatous" tissue, etc. In a similar manner, one type of epithelium may undergo change into another—a flattened epithelium may become cubical or columnar, or *vice versâ*; a layer of epithelium which is normally single may become two, three, or more layers deep, and so on. Again, the blood-vessels may be imperfect in their structure, and may, by their rupture, lead to hæmorrhage.

In the tumour itself, or in secondary growths from it, certain of the peculiarities and characteristics of the original tissue tend to reproduce themselves—usually, however, with easily recognisable variations, especially in their gross arrangement. Thus, the prickle-cells of the stratum Malpighii which proliferate in acanthomas or epitheliomas growing from the skin, etc. (Figs. 168–9, p. 336), are also found in the secondary growths in lymph-nodes, liver, etc. Saccular spaces, closely resembling those of the normal thyroid, may be reproduced in secondary growths following malignant disease of that gland;

and, similarly, gland-like spaces lined by columnar epithelium are common in metastatic growths, *e.g.*, in the liver, or in the bones or elsewhere, when these follow adeno-carcinomas of the stomach or intestine. Imperfect attempts at secretion and the reproduction of the structure of the mammary gland may be observed in tumours secondary to cancer of the breast. The typical columnar cells so characteristic of compound cystic ovarian adenomas are found in the secondary growths which frequently arise from the malignant forms of these tumours ; and innumerable other individual instances of the same general tendency might be cited.

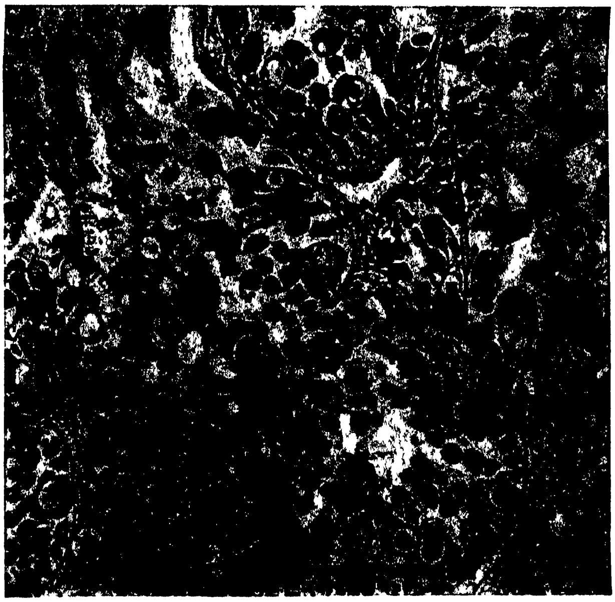


FIG. 126. *Phagocytosis by the tumour-cells of a bronchial carcinoma infiltrating the pleura.* Numerous " vacuoles " containing cell-inclusions (other tumour-cells, remains of leucocytes, etc.) are seen in various stages of intracellular digestion. Hæmatoxylin and eosin. × 150.

DEGENERATIVE CHANGES IN TUMOURS are extremely common. Nutrition is often locally deficient, leading to fatty, colloid and mucinoid degenerations, glycogenous infiltration, necrotic changes and calcification. Hæmorrhages into or from tumours are of frequent occurrence in many varieties of new growth, and may be due to rupture or injury, especially in the case of the imperfectly-formed vessels of sarcomas and gliomas : to infiltration and erosion of the tumour-cells into pre-existing vessels : or to necrosis and ulceration, or secondary inflammatory processes from bacterial infection.

PHAGOCYTOSIS IN TUMOURS. Tumour-cells are frequently actively phagocytic, and may englobe and digest red corpuscles, leucocytes, etc., sometimes in considerable numbers (Fig. 126 above and Fig. 740, p. 1150). The erosion of the tissues caused by malignant new growths is due in part to this phagocytic activity ; though various factors, such as the action of certain digestive enzymes produced by the tumour-cells, pressure, etc., probably play an important part in this process. Leucocytes and other wandering cells, especially of the large mononuclear variety, are also commonly seen attacking primary tumour, *i.e.*, secondary growths are the offsprings of the primary tumour, later, the process may continue by further metastases from the secondary and subsequent growths. There is, as already pointed out, almost always, in metastases, the persistence of some of the characteristics of the original tumour, either in type of cell or in general structure. There may, however, on the other hand, be considerable deviation from the cell-type found in the primary growth, *e.g.*, the cells may be larger in size and show alterations in structure. They may also grow much more rapidly. The metastatic growths may, in some instances, be more vascular. In others, they may be less pigmented than the primary tumour, *e.g.*, in some secondary growths in melanotic cases, pigment may be scanty or absent.

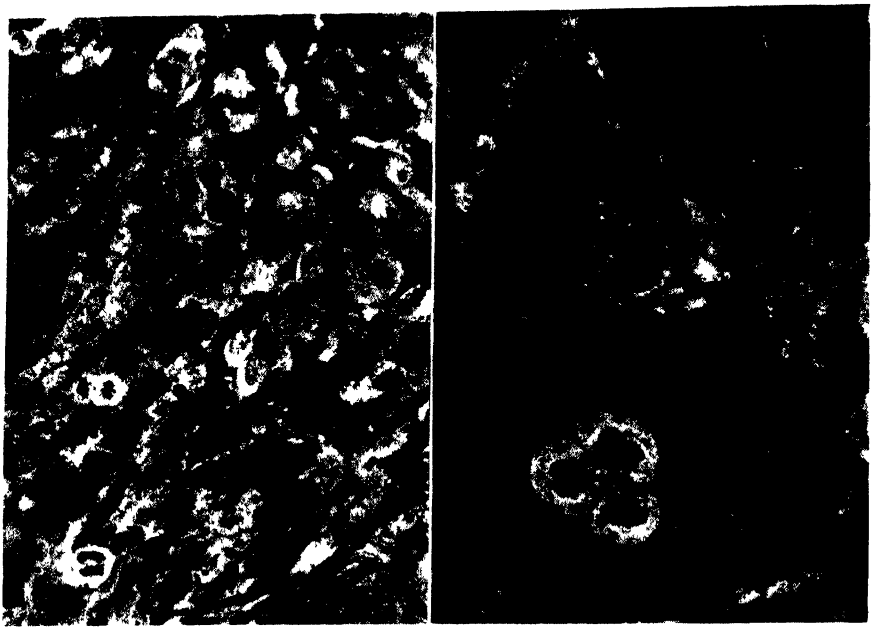
The mechanism of the secondary spread of tumours and **the invasion of other tissues by them,** is partly a **physical,** and partly a **vital,** phenomenon. For example, a fragment of tumour, a group of cells, or perhaps even a single tumour-cell, may become detached and sink down in the peritoneal or pleural cavity from the action of gravity or from the movements of the organs; or, in some instances, the spread may occur **by contact,** *e.g.*, between the opposite sides of a serous cavity, the lips or labia, with the consequent implantation of tumour-cells : or **by growth and carriage along lymphatic trunks,** as in the majority of carcinomas, *e.g.*, in epithelioma of the tongue spreading to the lymph-nodes of the neck. The walls of lymphatic trunks may themselves become extensively infiltrated. In other instances, the tumour may be disseminated by the **blood-vessels**—for example by the **veins,** especially in the case of tumours the vessels of which are very imperfect, *e.g.*, sarcomas; but this method of spread is also common in carcinomas, from the invasion of the vessel-walls, fragments of the tumours being carried away and giving rise to secondary growths in distant parts, especially in the liver or lungs. A reference to the possibility of the **retrograde** spread of tumours, as well as of bacterial infection, by veins, particularly those in connection with the vertebral column, will be found on p. 171. Spread by means of the **arteries,** *i.e.*, an **embolic** spread, is not by any means uncommon, and probably explains the widespread multiple new growths sometimes found in the bones and in other tissues. Myxo-chondromas may spread by direct growth along the interior of blood-vessels, especially of the veins, which may thus become filled by the tumour. Some types of tumour tend to metastasise to certain particular sites, *e.g.*, the bronchial carcinomas show a particular tendency to involve mediastinal lymph-nodes, the suprarenals and the brain. Other examples of apparent organ-selectivity of metastases are the skeletal deposits from renal carcinoma (so-called " hypernephroma ") and from carcinoma of the thyroid, breast and prostate : and the hepatic metastases of the melanotic growths.

It is an interesting point to note that certain organs, which are comparatively rarely the site of primary tumours, are, probably on account of their relations to the blood- and lymph-circulations, liable to the occurrence of metastases. Thus, the liver is exceptionally liable to become involved from primary carcinomas or sarcomas occurring in the other parts of the abdominal cavity which drain their blood into the portal vein, or the lymphatics of which are closely connected with those passing out at the hilum of the organ.

Similarly, the lungs, from their intimate association with the circulation, act as filters for the venous blood coming from all parts of the body, through the right side of the heart; and hence these organs are specially liable to involvement by tumour-cells which may have found their way into the blood-stream. In the same manner, the lymph-nodes are particularly liable to be invaded by the cells of carcinomas, which most frequently become disseminated by way of the lymphatic channels. Some organs, on the other hand, are remarkably immune from tumour-growths, both primary and secondary, for example, the heart and spleen, although these organs are both very freely supplied with blood.

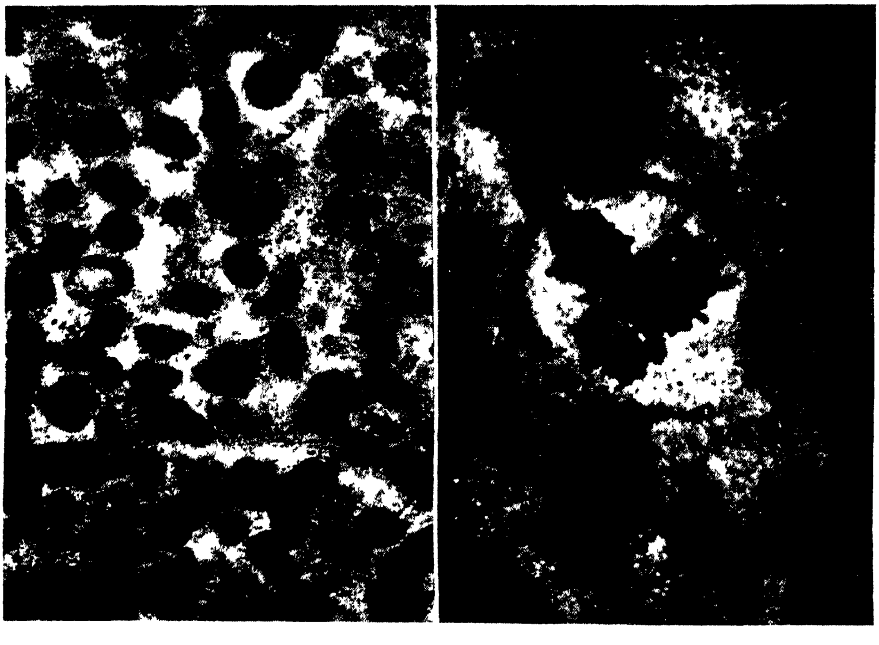
COMPONENT STRUCTURAL ELEMENTS OF A TUMOUR. In the examination of the histological structure of any given tumour, attention should be directed more especially to the characters of the **cells** and the **intercellular material.** It is sometimes a matter of difficulty to determine how far other component parts, such as **blood-vessels** and **lymphatics,** are to be regarded as concomitant rather than essential elements in a tumour.

Cells. Great variations are necessarily found in the nature and appearances of the cells of different tumours. As already noted, they, in many cases, tend to reproduce the characters—imperfectly and aberrantly it may be—of the cells of the original tissue. Thus, prickle-cells may be found in growths from squamous epithelium, hence the term "acanthoma" (*see* footnote, p. 337): glandular cells in those from glands: cells of connective-tissue type in those from the connective tissues, and so on. The term "**metaplasia**" has already been defined (p. 263) as the transformation of one tissue into another member of the same group, and examples of this type of change are of frequent occurrence in tumours. Another characteristic frequently exhibited by the cells of new growths, more especially in the malignant varieties, is the tendency to "**revert,**" or to become transformed into cells of a more primitive type developmentally; and, as a general rule, the more malignant the tumour, the more "primitive" or undifferentiated do the cells become. To take a concrete example, the simple tumour arising from fibrous connective tissue is a fibroma. In the "hard" fibroma, a slow-growing tumour, the cells are indistinguishable from the fibrocytes of any fully-formed fibrous tissue, the collagen-fibrils dense and thick, and the blood-vessels having fully-formed, though perhaps unduly fibrous, walls. In the "soft" fibroma—still a "simple" tumour, but one in which growth is not quite so slow as in the hard variety—the spindle-shaped cells or fibroblasts are broader or "plumper": their nuclei more ovoid than rod-shaped: the cytoplasm more abundant: and the interstitial fibrous tissue rather scantier, but the vessels still possessing definite walls. Again, in certain fibro-cellular tumours of very slight malignancy—the so-called "recurrent fibroids," or fibro-sarcomas—these more primitive characteristics may be rather more marked, and the blood-vessels thin-walled and poorly supported. Then, passing back through the series of sarcomas, as the type of cell becomes more primitive, *i.e.*, as we pass from the large spindle- and large round-celled varieties to the small spindle- and small round-celled tumours, the intercellular substance and blood-vessels also become progressively more and more imperfect, and the relative malignancy of the tumour



(A) × 400. (B) × 1250.

FIG. 127. Mitotic figures in a malignant tumour (an actively growing meningothelioma removed from a man aged 39). (A) High-power view showing numerous monaster and dyaster forms. In (B) is seen a triple mitotic figure under the oil-immersion. (Mr. F. Wilfred Willway's case, Bristol Royal Infirmary.) Phosphotungstic acid-hæmatoxylin.



(A) × 400. (B) × 1250.

FIG. 128. Mitotic figures in a fresh-wet film-preparation of a biopsy-specimen removed from the brain of a woman aged 42, the examination of which allowed of an immediate diagnosis of malignant metastasis (from a scirrhous breast-tumour removed two years previously but thought to have been completely excised). (A) High-power view showing numerous mitotic figures. (B) An irregular triple (or quadruple ?) mitosis seen under the oil-immersion. (W.E.H. case.) Toluidin blue.

increases. This malignancy reaches its greatest degree in the case of the completely undifferentiated or primitive small round-celled sarcomas, in which the cells are small and spherical, the intercellular substance extremely scanty, and the vessels represented by channels passing between the tumour-cells, in some cases apparently without even an endothelial lining. An analogous series of changes is well illustrated by the gliomas, and in this connection the diagrams on pp. 952 and 1098 will be found helpful. In other words, just as the individual human embryo may be regarded as recapitulating the developmental history of the race; and, just as we may now and again find a " throw-back " or reversion of the fœtus to a more primitive ancestor, so, in tracing back the character of the connective-tissue cells through this complete series of connective-tissue tumours, we find, as we pass from the simpler to the more malignant members of the series, a reversion,[1] as it were, to an earlier type of connective-tissue cell. It is to this tendency of reversion to a more ancestral type of cell that the name **anaplasia** is applied (*see also* p. 285).

Tumour-cells may show, not only great deviation from the cell-type characteristic of the original tissue from which the tumour is growing, but they may also, in the same tumour, show endless diversity among themselves. Thus, there may be great variations in the shape and size of the cells, and in the characters and method of division of their nuclei. Multipolar and other irregular and unequal forms of mitosis are of frequent occurrence (Figs. 127 and 128). Moreover, the cells of a tumour may show very rapid and aberrant reproductive activities, or equally rapid and excessive degenerative changes, more especially in their nuclei (karyolysis, karyorrhexis, etc.).

The intercellular material varies greatly in its amount and nature in different tumours. Thus, in new growths of connective-tissue type, it may vary from the clear, homogeneous, jelly-like matrix seen in some myxomas, or the very scanty and imperfect fibrillation of the more malignant types of sarcoma, up to the fully-formed dense fibrous tissue of the hard fibroma. In these tumours, the cells are each separated from one another by the intercellular material; whilst in the carcinomas and other varieties of epithelial tumour, and also in some types of endothelioma, the neighbouring cells of each cell-group usually remain in contact with one another, the whole group being surrounded by a stroma derived from the pre-existing connective tissue of the part. Certain tumours give rise to great irritation and proliferation of this pre-existing connective tissue—for example, the " scirrhous " varieties of cancer, which indeed owe their name to the hard and dense character of the tissue thus produced.[2]

In the case of the simple tumours, there is usually, around the tumour, a condensation of the proliferated connective tissue of the organ or tissue in which the tumour is growing. As such a simple growth increases in size, it pushes aside the surrounding tissues. It usually possesses a distinctly demarcated margin, outside which the proliferated fibrous tissue may form a definite capsule, enclosing and separating the tumour from the surrounding tissues. Though the presence of such a capsule is characteristic of the simple tumours, it is not invariably found around them; and, conversely, although malignant growths usually possess margins which are very indefinite, owing to the infiltration of the surrounding tissues by the tumour-cells, yet one may occasionally meet with examples of encapsulated malignant tumours. **Encapsulation of a tumour** *depends on several factors, of which the more important are the power of infiltration and rate of growth of the tumour on the one hand, and ease of compression and power of reaction in the tissue involved, on the other.*

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[1] *See* footnote on p. 285.

[2] From the Greek adjective *σκῖρος* or *σκιρρός*, *skiros* or *skirrhos*, hard, hence *τό σκῖρον*, *to skiron*, the hard rind of cheese, and the substantive, *σκῖρος* or *σκίρρος*, the hard substance, gypsum, and hence metaphorically any hard swelling or tumour, Latin derivative, *scirrhus* : *cf.* the Greek word *σκληρός*, *sklēros*, hard, hence the terms " sclerosed " and " sclerotic."

In the general definition of a tumour given on page 269, it was stated that a new growth is devoid of nerve-control, i.e., is "autonomous." Apart from neoplasms of nerves themselves, nerve-fibres are found in certain tumours, but, except in the case of some of the teratomas, they are probably those that pre-existed in the original tissue, and which had merely become surrounded by and incorporated in the neoplasm, and are, therefore, not of new formation. Whatever view be taken on this subject, the fact remains that tumours are *not* under the normal control of the nervous system, as are the tissues in which they grow. In other respects, also, tumours exhibit autonomy, as by their failure to participate to a degree equal to that of normal tissues in the metabolic activities of the body. This is well exhibited in the cases where patients suffering from lipomas or fatty tumours are attacked by some disease which produces general emaciation and absorption of the body-fat, the bulk of the tumours remaining unaffected.

Blood-vessels and Lymphatics. In addition to the tumour-cells proper (*e.g.*, epithelial cells, non-striped muscle-cells, sarcoma-cells, etc., according to the variety of tumour), new growths of necessity contain other elements which may not be constituents or parts of the tumour proper, but are to be regarded rather as an accompaniment or a consequence of its growth.

In the case, however, of the hæmangiomas, or neoplasms composed of blood-vascular tissue, the blood-vessels are, of course, the essential constituents of the tumour, and not merely a consequence of its growth.[1]

Tumours, for their growth and maintenance, require a sufficient blood-supply, and this they obtain by means of new vessels formed from those in the neighbourhood of the tumour. These newly-formed vessels are sometimes very imperfectly developed, *e.g.*, in sarcomas, in which they may consist merely of a single layer of endothelium, or even of apparently unlined spaces and channels among the tumour-cells. In the latter case, the tumour-cells may easily break off and pass into the circulating blood, and be carried to distant parts—a fact which explains the general tendency of sarcomas to be disseminated by the blood-stream. This imperfect character of the blood-vessels in sarcomas also explains the great liability to the occurrence of hæmorrhage, and of various degenerative and necrotic changes in these neoplasms. In other tumours, again, the blood-vessels are well-formed and, it may be, fully developed. In the case of carcinomas, for example, the vessels of the tumour are to a large extent those of the tissues amongst which the cancer-cells are infiltrating, but such tumours also contain new vessels formed by a process apparently identical with that which occurs in inflammation and repair. Hæmorrhages are also of frequent occurrence in carcinomas, but are due usually to the erosion of the walls of the vessels by the infiltrating malignant cells. Degenerative and necrotic changes are common in cancerous tumours, especially in those of rapid growth, owing to the tendency of the tumour-mass to outgrow its blood-supply.

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[1] For the formation of blood-vessels and vascular spaces in meningiomas, *see* pp. 1084–5.

Newly-formed lymphatics are abundant in some tumours, for example in carcinomas, and it is especially by the lymphatic channels that these tumours are liable to be disseminated, although it should be noted that the spread of carcinoma by the blood-vessels is not by any means an infrequent occurrence. In some special instances, the newly-formed lymphatics are themselves the essential elements of the tumour, *e.g.*, in lymphangiomas. It is sometimes difficult, and indeed frequently impossible, to determine whether the lymphatics of a given tumour are newly developed, or have been pre-formed in the original tissue.

The presence of leucocytes and other wandering-cells, especially of small lymphocyte-like cells, in tumours, more particularly near the spreading margin, is probably a secondary phenomenon due to the irritation of the tumour, and is in all likelihood to be regarded as an attempt at defence and repair. Collections of **phagocytic monocytes** or **macrophages,** *e.g.*, in the form of "**foam-cells,**" are common in meningiomas and gliomas (pp. 1084–5 and 1106). In other cases, such leucocytic infiltration may be due to the secondary inflammatory changes produced by invading bacteria, this being common especially in tumours growing at the surface of the body or in the wall of the gastro-intestinal canal, etc. ; *i.e.*, in positions specially liable to the attack of micro-organisms. In such inflamed tumours, polymorphonuclear leucocytes are often numerous.

THE CHEMISTRY OF TUMOURS

Investigation of the chemistry of tumours may well afford an important field of work in the future. At present there is little definite knowledge concerning the chemical processes which occur in living tissues, whether normal or neoplastic ; the changes which take place appear to be of a complicated nature, however, and some of the variations from the normal which have been observed in neoplastic tissues may be summarised as follows.

Phosphorus and iron have a similar distribution in normal and in neoplastic tissues and the quantities present are proportional to the amount of nuclear material in the tissue. Potassium is, however, present in greatly increased amount in the case of rapidly-growing tumours, whilst calcium is correspondingly decreased, so that the ratio between these inorganic constituents shows considerable alteration in malignant disease.

Protein substances appear to be unaltered as to their nature in tumour-cells, but nucleo-proteins are especially abundant in highly-cellular tumours, as might be expected. The products of protein-hydrolysis are found also in tumours and, since the metabolism of many tumours is more active than that of normal tissues, there is some tendency for these products to enter the circulation and in certain cases to cause disturbances due to their presence. Thus in multiple myelomatosis, "Bence-Jones protein" may appear in the urine (p. 319).

Extending the field of simple chemical observations to the more important one of actual metabolic activities, Warburg was able to demonstrate the phenomenon of aerobic glycolysis as being common to the majority of malignant tissues. Warburg's work showed that, whereas normal tissues will always utilise oxygen, if it is available, in order to oxidise glucose to carbon dioxide and water and so produce energy. and will resort to the process of glycolysis (*i.e.*, the breaking down of glucose into lactic acid) only if oxygen is absent : yet malignant tissues almost invariably break down glucose to lactic acid by the process of glycolysis even though abundant oxygen is present. Moreover, malignant tissue possesses far greater powers of anaerobic glycolysis than normal mature tissues and so is able to survive better than the latter when the oxygen-supply is deficient.

These differences of behaviour on the part of malignant tissues from that of the normal, imply that individual cells have lost their normal cellular respiratory function, and in consequence oxidation of glucose does not take place in them.

THE INCIDENCE OF TUMOURS IN GENERAL

Though, as we have stated, the essential cause of new growth is still entirely unknown, certain hypotheses have been advanced to account for the direct causation of neoplasia, and many of the indirect or predisposing causes are well recognised and may be summarised as follows :—

1. **Age.** It is an established fact that the liability to carcinoma tends to increase as life advances, though children and young adults are not by any means exempt. There is also with advancing years a similar increased liability to sarcoma, although this variety of malignant disease is commoner than carcinoma in the earlier periods of life. Carcinoma itself does not become a formidable cause of death until after the age of thirty-five ; and at seventy-five it is a thirty times more frequent cause of death than at thirty-five.

This increased liability to malignant disease with advancing age may be due to various factors, such as—(i.) Progressive lowering of the vitality of the tissues, with a consequent diminution of the power of resistance to invasion. (ii.) Loss of control over the formation of new tissue. (iii.) Variations in the vegetative vitality or power of reproduction and growth of the different tissues, *e.g.*, one tissue retaining more power than another, and so tending to invade the other. It is a well-established fact that malignant disease tends to occur in organs especially at periods when their functional activity begins to decline—for example, during the involution of the prostate gland, breast and uterus.

2. **Sex.** Malignant disease is relatively commoner in the female than in the male—roughly, in the proportion of 3 : 2—largely on account of the comparative frequency of mammary, uterine, and ovarian tumours. On the other hand, teratoid tumours of the testis are much more frequently malignant than are the corresponding tumours of the ovary.

3. **Family Predisposition.** Heredity appears to play some part ; though whether this is due to a decreased family-resistance, or to an actual predisposition to the disease, or, again, to the presence of some possible infective cause, is as yet quite unknown. Members of some families may show a tendency to die of cancer or other forms of malignant disease at a certain age. It must be remembered, however, that, after the age of thirty-five, one female in every eight, and one male in every twelve, die of cancer annually, and thus few families of any size are likely to escape its incidence. Many of the multiple-tumour syndromes are definitely familial in their incidence, *e.g.*, polyposis of the intestines (p. 756), multiple neurofibromatosis (pp. 301 and 1135) and tuberous sclerosis (pp. 315 and 1134 *et seq.*).

4. **Race.** Some races of mankind are more liable than others to certain forms of tumour ; and the same fact appears to be true of the lower animals.

For example, white horses are said to be more liable to the occurrence of melanoma than are those of other colours ; and experimental inoculation with Jensen's tumour, as well as the induction of tumour-formation *de novo* by carcinogenic agents (pp. 282 and 287), has been more successful in some strains of mice than in others. Nationality and civilisation appear, however, to have little influence upon liability to malignant disease in general. Similarly, mammals, amphibians and fishes, wild and domesticated animals, are all subject to tumour-growth.

5. **Occupation.** There is in some trades an increased liability to cancer : for example among chimney-sweepers, paraffin-workers, aniline-dye workers, and others exposed to the influence of special irritants. (*See below, under* " Local irritation ".)

6. **Environment.** Certain countries, districts, and even certain houses (the so-called " cancer-houses "), are sometimes spoken of as predisposing their inhabitants to malignant disease, but, in the individual cases usually cited, it is quite possible that there may have been other predisposing factors at work, such as heredity, longevity, weakened resistance produced by other diseases, etc. Obviously, any region from which the young people have migrated for economic reasons will appear to be a " cancer district " because a large proportion of the remaining population is in the age-period of special liability to cancer.

Many other alleged causes, often but little supported by evidence of any value, have been put forward from time to time, as, *e.g.*, over-feeding, special articles of diet, etc. ; and there is almost no food-element which has not at some time or other been alleged to play a part in the production of malignant disease.

ÆTIOLOGICAL FACTORS IN TUMOUR-FORMATION

Some more direct causes appear to have a definite influence on the formation of certain tumours. Such causal factors are, therefore, worthy of consideration, and may have a wider application than is at first apparent. Of these, " local irritation " and " trauma " are the most generally recognised.

1. **Local irritation,** either physical or chemical (*cf.* p. 287), seems in some instances to have an undoubted causal relationship to the disease, and appears in such cases to stimulate tumour-growth, perhaps in a way somewhat analogous to that by which it may produce excessive reparative processes. It is impossible at present to say whether prolonged irritation may of itself produce new growth in suitable subjects : or whether it merely prepares the way by weakening the resistance of the tissues locally, and so produces a suitable soil in which some other specific agent may then the more easily cause tumour-formation, particularly if associated with excessive reparative processes in the damaged tissues.

Be this as it may, chronic irritation certainly does appear to possess some definite causal influence upon the growth of tumours, as in the case of "**chimney-sweepers' cancer,**" mentioned above, where the long-continued irritation, especially of the scrotum and neighbouring parts, by the accumulated carcinogenic soot-particles, may ultimately lead to the development of an epithelioma. Similarly, epithelioma of the lip and tongue is said to arise from the long-continued use of a short clay-pipe—the so-called " **smokers' cancer** " ;

and certainly in the past (the clay-pipe is now but little used) the enormous preponderance of the disease in this position in the male seemed to lend support to such a view. Cancer may follow prolonged irritation by a sharp or jagged tooth, or by the plate supporting artificial teeth. Chronic ulcers in any situation and scar-tissue or cheloid may ultimately become the seat of new growth. Cancer may also supervene upon syphilitic leukoplakia of the tongue, and gliomas develop around old-standing gummata of the brain.

There is little doubt that certain chemical irritants, for example some of the products of the destructive distillation of wood and coal, such as tar (*cf.* p. 287), soot and paraffin, can, by their prolonged application to the skin, *e.g.*, in the case of workers who deal with these substances in their trades, lead to epithelioma of the skin.[1] Epithelioma can supervene upon the hyperkeratosis caused by the prolonged administration of arsenic. Workers in aniline dyes (especially the group containing saffranin, eosin, fuchsin, congo-red, benzopurpurin, etc.)—both dye-makers and dyers—appear to be unduly liable to cancer of the bladder. The injection of fat stained with scarlet-red under the skin produces active epithelial proliferation, and an ointment containing this dye is now often used therapeutically to stimulate epithelial growth on ulcerated surfaces. For a note on the successful induction of intracranial tumours in mice by the implantation of methylcholanthrene, *see* p. 1128. The treatment of the cells of tissue-cultures from inbred strains of tumour-sensitive mice with methylcholanthrene, 3 : 4-benzpyrene and other carcinogenic hydrocarbons has, so far, been negative in producing any ascertainable malignant changes in the artificially-grown cells.

2. **Direct mechanical injuries** (apart from an oft-repeated series of slight traumata, especially if applied to a sensitive tissue such as the skin) may also predispose the tissues to tumour-growth, possibly owing to the laceration and consequent intermingling of the different tissue-elements : or perhaps by merely lowering their vitality and power of resistance. Patients suffering from tumours of the breast, brain, testicle, etc., when they consult their medical adviser, almost always come with a definite history of injury ; and, though it is, of course, possible that an injury may have been a predisposing cause of the condition, it must not be forgotten that such a tumour may have previously existed in the tissue, and the accident might only have served to draw the patient's attention to it for the first time, for it is well recognised that, in its earlier stages, malignant disease is often painless, and tumours may, therefore, exist for a considerable time without attracting attention.

In matters of industrial compensation it is often assumed on very slender grounds that a particular mechanical injury has been the cause of the growth of a neoplasm. In order to establish this to even a reasonable degree of certainty it should be shown : (1) that there was no tumour before the injury ; (2) that the new growth appeared within a reasonable time after the injury, neither too soon nor too late ; and (3) that the disease arose in the precise region in which the injury was sustained. When compensation is claimed for the acceleration of the growth of a tumour known to have been present before the injury was sustained, a still more difficult question is raised. It is generally assumed that an injury applied directly to the tumour, and of such a nature as to increase its blood-supply, could cause it to grow more rapidly than would otherwise have been the case.

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[1] In the report of the Departmental Committee on Compensation for Industrial Diseases (1907), the mortality for cancer among chimney-sweepers is given as twice that among occupied males generally.

Southam and Wilson ("Cancer of the Scrotum," *British Medical Journal*, 1922, ii, 971) call attention to the prevalence of scrotal cancer among the "mule-spinners" in South Lancashire, and attribute it to chronic irritation as the result of friction and contact with oil to which this occupation exposes this part of the body. They also suggest that the mineral oil employed is analogous to soot, tar, paraffin, etc., all of these being products of the dry distillation of coal. (*See also* "Mule-Spinner's Cancer," by E. M. Brockbank, *Brit. Med. Jour.*, 1941, i, 622.)

Sarcomatous tumours of bone are sometimes described as following upon fracture, but here again it must be borne in mind that the sarcoma may have been present previously, and may thus itself have predisposed to the production of the fracture. The occurrence of epitheliomas and of sarcomas arising from the margins of old ulcers and from scars has already been mentioned, and may conceivably be due either to chronic irritation or to actual displacement and intermingling of the tissue-elements. Similarly, cysts of the iris have occasionally been recorded as following punctured wounds of the eye, and have been regarded by some writers as due to transplantation of corneal epithelium or other structure at the time of the accident.

HYPOTHESES CONCERNING THE ORIGIN OF TUMOURS

Many of these are of historic interest only, but all of them are instructive, since they each tend to centre around one or more of the observed " facts " concerning tumours.

1. **Hypothesis of Waldeyer and Thiersch.** These authors recognised the fact that the cells of a carcinoma are derived from those of covering and secretory epithelium. Under normal circumstances, according to their hypothesis, there is a state of equilibrium or balance between the epithelial and the connective tissues with regard to their respective proliferative capacities, each holding the other in check. Overgrowth of the epithelium is thus, they say, prevented by the influence of the connective tissues. With advancing age, however, they postulate a progressive weakening and loss of this restraining power on the part of the connective tissues, with a consequent freeing, as it were, of the epithelium, which can then proliferate and give rise to tumour-growth, reversion to a more primitive type of cell occurring at the same time. They thus endeavour to explain the increasing liability to cancer with advancing age. The main objection to this hypothesis appears to be that, were this the true explanation of cancer, the occurrence of multiple primary foci should be the rule, instead of, as is actually the case, the exception, in malignant disease.

2. **Cohnheim's embryonal hypothesis,** or " **theory of embryonic residues** " or " **resten,**" is grounded on the view that, early in development, some tissue-rudiments—embryonic cells, or portions of embryonic or fœtal structures—may have become caught or have intermingled in other tissues, where they remain dormant, but retain in latent form their inherent embryonic capacity for unlimited proliferation, and are thus, under favourable circumstances, capable later of taking on new growth, and so leading to tumour-formation. Though this hypothesis obviously does not account for the production of all tumours, it is certainly a possible explanation of the mechanism by which some neoplasms arise, though it affords no clue as to the nature of the factors which stimulate

the new growth of the latent "residues." The hypothesis is in many ways analogous to the "heterology" one of Virchow, who similarly suggested that a portion of one tissue might become entangled in another by a process of intermingling during development, or from injury or disease.

3. **"Tissue-tension" Hypothesis of Ribbert.** This hypothesis is really a combination of the two described above, since Ribbert accepts the views of Waldeyer and Thiersch as to the existence in health of a balance or tissue-tension between the various tissues and tissue-elements, whereby there is a mutual check against undue proliferation of any particular tissue. According to Ribbert, the tissues most likely to be freed from this normal control are those which, from developmental errors, or as a result of injury or disease, have become intermingled with the normal tissues of the body. Thus it is easy to account for the proliferation of misplaced adrenal tissue present in the kidney as an embryonic residue—a phenomenon less common, however, than was formerly supposed (pp. 848 and 895) : or of islets of cartilage misplaced as a result of early rickets ; but the hypothesis fails to provide any reasonable explanation if it is extended to tumours in general.

4. **The Inclusion of One "Individual" within the Tissues of Another, giving rise to the Teratomata** (p. 351). This, again, cannot be considered a hypothesis which explains the origin of all tumours, though there have been attempts to extend it in a general way by postulating that many tumours are in reality teratomatous, even although histologically they may appear to contain a single tissue only. Teratomatous tumours appear to result from the inclusion of a pluri- or toti-potent cell, or cells within the tissues of another individual ; and, from the after-proliferation of this included cell, many conditions may arise, varying from the most rudimentary true teratomatous dermoid cysts, through the series of those containing skin, hair, sebaceous glands, teeth, etc., and even bones and organs, up to parasitic or adherent twins in all stages of development. To the more imperfect forms of such tumours the term "teratoid" has sometimes been applied (p. 351). A complete series can be demonstrated, from the simplest "dermoid cyst," through the complex teratomas and the united double monsters, to the free-living identical twins. When sex is determinable, the components of a double monster are always of the same sex, as are uni-ovular twins. It is reasonable to consider that all the abnormalities of this general nature are of uni-ovular origin. Into a full discussion of the ætiology of double-headed and other monsters, and as to whether their formation is due to double-yolked or to binuclear ova, to incomplete fission of the germinal area of one embryo, or to the partial fusion of the germinal areas pertaining to twins, it is not possible to enter here, but upon these and allied and analogous problems some of the recent discoveries of **experimental embryology** may be found to have an important bearing (pp. 291–3).

In this connection it is of interest also to note that similar or identical tumours may occur at or about the same age in human twins, especially **identical twins**. Dr. Madge T. Macklin[1] (of London, Ontario) has analysed the records of a series of such twins in which both members developed tumours. Of thirty-four pairs of identical twins, thirty-two showed the *same* kind of tumour in the *same* organ, whilst two had tumours of different kinds. Where the time of onset was known, the average difference in the ages of the two members in the case of identical twins was only 1·3 years.

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[1] "Human Genetics : Seventh International Congress," Edinburgh, August, 1939. *Lancet*, 1939, ii. 664.

5. **Hansemann's Hypothesis of "Anaplasia" in Tumour-cells.** All cells possess two classes of activity :—

i. The faculty of multiplication.
ii. The capacity of individual growth—*i.e.*, increase in size—and the development of specialised function, with specialised structural peculiarities to correspond.

The former of these—the faculty of cell-multiplication—is found in its most active form early in life, and more especially in the tissues of the embryo, in which the activities of cell-division are far in excess of those connected with specialised function ; whilst, as age advances, the reverse is the case, the capacity for specialised function becoming emphasised at the expense of the more primitive faculty of multiplication. Now if, for any reason, this proliferative activity (the so-called "embryonic" character) of the cells should be re-established, the condition may be regarded as a reversion to the more primitive type of cell ; and it is to this process of reversion which appears to take place in neoplasms that Hansemann has applied the term **anaplasia,** to which reference has already been made.[1] The greater the degree of anaplasia, and the more primitive and undifferentiated the type of cell, the more malignant, as a rule, is the resulting neoplasm. The less marked the anaplasia of the cells, the more "benign" or "simple" is the resulting new growth. Between these two extremes there may be found, as is pointed out on pages 275–7, tumours exhibiting all gradations of "innocency" and "malignancy." The fact of these transition-stages between innocent and malignant tumours is well recognised by all pathologists, and seems to indicate that, in endeavouring to discover the ultimate cause of tumour-growth, attention should be directed, not only to the malignant, but also to the simple, neoplasms.

Parasitic Hypotheses of Tumour-formation. All the foregoing hypotheses have dealt rather with the mechanism than with the intimate and essential cause of tumour-growth. Innumerable attempts have been made to demonstrate the presence of some organismal cause for the disease, and, as a result, numerous "cancer-parasites" have from time to time been described, but none of these has had its claim as a causal agent established. Many of the alleged parasites have been shown to be merely cell-inclusions or degeneration-products, whilst others have been proved to be associated bodies without any relation to the ætiology of the disease. It must, however, be recognised that lesions very similar to tumour-growth are caused by known parasites, *e.g.*, the papilliferous cysts produced in the livers of rabbits by *Eimeria perforans* or *E. stiedæ* or *Coccidium oviforme*—(p. 375, and Fig. 199, p. 376) ; and, in consequence, although the present tendency is to abandon the search for gross parasites, there still exists the possibility of the ultra-microscopic viruses (pp. 123 and 287–8) as the cause of malignant disease, either alone or in combination with other factors such as the potentialities—"embryonic" or otherwise—of the cell itself.

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[1] It might, perhaps, be more accurately defined as *a progressive loss of acquired characters* —*i.e.*, a process of "*de-differentiation*" (*see* pp. 277 and 1097).

EXPERIMENTAL CANCER-RESEARCH

1. **The Propagation of Malignant Disease in Animals.** One of the difficulties in the experimental study of malignant disease is that the forms in which this occurs in man are relatively uncommon in the lower animals, and, further, it has so far been impossible to transfer such growths from man to the lower animals. Workers must content themselves with the experimental use of certain types of tumours which occur spontaneously or which are produced experimentally in animals, and even these can be transferred only to other animals of the same or a closely allied species.

Study of these transplantable tumours in animals has, however, yielded valuable information, not the least of which is the observation by Jensen that the transplanted tumour survives, in whole or in part, and that it is the proliferation of these surviving cells which gives rise directly to the new tumour. Such a tumour continues to develop in the grafted animals, and there was, apparently, in these experiments, no question of any malignant transformation of normal cells of the animal's own body giving rise to the tumour-mass. In this manner, true transplantations of tumours can be shown to take place and the classical tumour-strains employed in the various research-laboratories are to be regarded as being formed of cells directly descended from those of the original tumour (but in this connection *see also* p. 288).

A transplanted tumour acts as a foreign body in the tissues, and is therefore likely to be attacked by phagocytic cells in an attempt to remove it. Moreover, the transplanted tissue may become infected by bacteria, so that suppuration occurs ; and this is liable to happen especially if the transplanted tumour is of considerable size, for the necrosis which is then almost inevitable will favour the growth of any micro-organisms present.

The pioneer of careful histological work concerning the transplantation of tumours was **Jensen,** who showed, as we have noted, that the tumour resulting from a transplantation is formed as the result of multiplication of certain tumour-cells from the implant itself and *not* as the result of any reaction in the cells of the host's own tissues. Jensen's conclusions in this respect, have been confirmed and extended by **B. R. G. Russell** (1908), who showed that the survival or destruction of a tumour-implant depends largely upon the type of " stroma-reaction " put up by the host's tissues. If the tissues of the host provide an active stroma which infiltrates the tumour-implant, then the latter will survive ; but, if no such stroma-reaction occurs, leucocytes will make their way into the tumour-implant and lead to the rapid or ultimate destruction of the latter. **Haaland** and **Russell,** of the Imperial Cancer Research Fund Laboratories, London (1908 and later), claim that, in the development of transplanted tumours, there is a tendency for the epithelial tumours to undergo such a variation of tissue-structure that they assume the undifferentiated cellular arrangement which is characteristic of sarcoma. This change is comparatively rarely seen and generally only after several generations of growth have taken place. It is doubtful how far such an observation may be taken to support the idea, held by some workers, of the possible recurrence in man of an epithelial cancer coming to have the histological appearances of a sarcoma. Study of human bronchial carcinoma has taught the need for caution in the interpretation of histological appearances, since these growths long puzzled pathologists, some regarding them as sarcomas, others as carcinomas, and others as endotheliomas (pp. 569–573).

2. **Carcinogenesis by Irritants.** For many years it has been recognised that, in man, chimney-sweeper's cancer, mule spinner's cancer and the epitheliomatous growths in X-ray workers appear to result from the long continued and oft-repeated action of specific irritants.

In 1913, **Fibiger,** of Copenhagen, showed that carcinomatous growths could be produced with comparative ease in the stomach of rats by feeding them on cockroaches infested with a nematode worm, *Spiroptera neoplastica.*

Some two years later, **Yamagiwa** and **Itchikawa** were successful in producing carcinomatous growths on the inner surface of the ears of rabbits by painting the part repeatedly with tar over a period of many months. Since the site chosen was one in which spontaneous growths of carcinoma do not occur, it was obvious that these workers had succeeded in producing malignant disease by means of a chemical irritant. The growths were, moreover, shown to be genuine malignant tumour-formations, since metastases resulted.

The subsequent work of **Tsutsui** indicated that mice are even more susceptible than rabbits to so-called " tar-cancer," and much work has resulted and information been accumulated concerning this particular type of tumour. It is now generally held that the carcinogenic substances responsible for these growths are derivatives of dibenzanthracene (*cf.* p. 282), but the matter is complicated by the fact that an optimum stimulation by the carcinogenic agent is necessary rather than a mere haphazard application of the substance concerned. The development of malignancy appears to be a slow and transitional process through the stages or phases of **chronic irritative overgrowth** : and then of **" simple,"** and finally, if the application of the irritant be continued, of definitely **malignant, papillomatous tumour-formation,** leading not only to local infiltration but also to the production of metastases. A similar slowly produced series of events ending in malignancy can be produced experimentally in the **" Shope skin-papilloma "** of the rabbit's ear—a **viral disease** (p. 123) in which the changes in the cells appear to show first as an irritative " pre-cancerous " stage, then passing through that of a simple, and, finally, of a malignant, papillomatous tumour—either gradually or, as some believe, by a series of steps or " cell-mutations," which can be hastened by trauma or by the application of other irritants such as the injection of scarlet-red.[1]

3. **Immunity-Experiments in Relation to Cancer-Research.** The belief in the so-called parasitic hypotheses in relation to malignant disease, and the experimental work in connection with the transplantation of tumours, led to the consideration of the immunological factors at work in connection with tumour-formation.

As with bacterial and virus-produced infective processes, **immunity to neoplastic conditions** appears to be of two main types, **natural** and **acquired.** Experimental work has proved that animals of different races, within the same species, may be **naturally immune** to tumour-transplantation. Attempts have been made to break down this natural immunity, but so far without success, though in the course of the experiments evidence has been obtained to show that animals from a tumour-bearing stock are more susceptible to tumour-formation following attempted transplantation than are animals from a stock untainted with tumour-formation whether natural or experimentally acquired. Age also has an influence, the younger animals being the more susceptible.

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[1] " Development of the Malignant Tumour," *Brit. Med. Jour.*, leading article, 1941, i, 933.

In the neoplastic processes, passive immunity does not seem to exist, but an active acquired immunity can be established under a number of differing conditions. The more important examples of such experimentally-produced active immunity are those which result from inoculation with tumour-cells, wherein, whether the tumour " takes " or not, an immunity, presumably of a specific type, may develop : secondly, those resulting from the injection of red corpuscles, embryonic tissues, or cells of the reticulo-endothelial system, *e.g.*, of the spleen, from an animal of the same species, whereby an immunity of non-specific type is conferred.

When actual tumour-cells are inoculated in an attempt to establish an immunity, the results obtained differ widely in different instances. A definite or even complete immunity to tumours of the type used for the inoculation may be produced, or no immunity at all may follow the inoculations ; whilst in some series of experiments it would appear that, although no immunological response is obtained against the tumour already successfully transplanted, yet there is inhibition of the growth of any further transplant of a tumour of the same type.

When any appreciable degree of acquired immunity does result from the injection of normal tissue-cells of an animal of the same species, in an attempt to induce resistance to tumour-transplantation, the immune state is very transient, though it may be active and efficient for the short time that it lasts. The most effective tissue for the purpose is embryo-skin, and, when this is used, the immunity established is certainly of high degree as regards further transplantation, though without any effect whatsoever on any tumour previously present, no matter whether this was of spontaneous origin or the result of a previous transplantation.

4. **The " Filtrable " Tumours** (*cf.* pp. 96, 123 and 285–7). Reference has already been made to the work of Jensen concerning tumour-transmission, and as a result of this work it was for some time believed that tumour-formation could result only when transplantation of actual tumour-cells had been carried out, so that in every case the resulting tumours were merely parts of the tumour from the previous host. Experiments concerning the carcinogenic action of tar have, however, proved that tumours *can* arise from stimulation of the animal's own cells. In 1911, Peyton Rous showed that he had been able to transmit malignant tumours in the case of the fowl by means of cell-free filtrates. The tumour which gave this important result is the now well-known " Rous fowl-sarcoma No. 1."

So far, the great majority of the filtrable tumours have been found in birds,[1] but the growths have the usual characters of malignant tumours in general as regards their capacity for invasion and spread. Such tumours undoubtedly arise in the bird from cells in which new growth is stimulated by the cell-free filtrate containing the " virus." Of the exact nature of this " virus " little is yet known, though the available evidence is in favour of its being particulate and of the nature of a living virus rather than an enzyme, as the fraction containing it can be separated by repeated or prolonged high-speed centrifugalisation, although the virus-particles are apparently not the only constituents of the centrifugalised deposit, which contains also (probably normal) particulate substances derived from the cells of the host.

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[1] In this connection, *see also* footnotes on pp. 123 and 625 *re* the possible production of leukæmia (as well as of sarcoma-like tumours) in fowls by filter-passing organisms.

5. **Viral Infections (continued).** **Gye** and **Barnard** in 1925 put forward what was claimed to be a complete elucidation of the mystery concerning malignant disease in general. This work is now recognised as important, since it serves to show the connection which may well exist between the viral and the cellular hypotheses of malignant disease in general, and the "Rous fowl-sarcoma," on which the work was done, in particular: and it appeared to suggest that, in the genesis of a tumour, two agents might be necessary in place of the single cause previously usually taken for granted. Of the two factors so postulated, one was thought to be **a living virus** common to all types of tumours; whilst the second, **the "specific factor,"** was assumed to be in nature chemical and peculiar to each tumour-type. Interesting as this work may have been, it must be remembered that, when the experiments with the Rous-tumour were repeated by other workers, the results described by Gye and Barnard were not fully confirmed, so that the hypothesis which these workers propounded concerning the presence of *two* factors in the production of malignant disease still awaits further investigation.

6. **The Relationship of Hormones to Tumour-Growth.** The changes produced in the breast and the uterus by the action of **œstrone** are mainly proliferative in character—dilatation of ducts, hyperplasia, and sometimes metaplasia, of epithelium and proliferation of acini. This overgrowth, at first only hyperplastic, may progress farther and may reach the stage of neoplasia, perhaps malignant in character. It has also been established that similar œstrogenic and carcinogenic reactions can be induced by the introduction into the body of certain hydrocarbons, especially those related to the sterols, *e.g.*, ergosterol. It is not surprising, therefore, that in the females of certain strains of mice particularly susceptible to the spontaneous occurrence of cancer of the breast, adenocarcinoma of that organ has been induced by the prolonged administration of **œstrogenic hormones** and also of certain chemical substances allied to these. The males of such strains are *not* spontaneously subject to the development of such breast-tumours, but it has been found that adenocarcinoma can be induced in as many as 80 or 90 per cent. of these males by the injection of œstrone, as well as of certain of the carcinogenic hydrocarbons (section 2, p. 287). Enormous scrotal hernias, and also lesions of the testis, including both benign and malignant new growths, have been induced in some strains of mice not naturally subject to these, by the prolonged administration of œstrogens.[1] Similarly, a variety of epidermoid epithelioma of the vagina and cervix uteri has been induced in a proportion of female mice by the injection of œstrone, and this particular tumour can then be propagated by transplantation from mouse to mouse. In both male and female rats of strains *not* naturally susceptible to its occurrence, adenocarcinoma of the breast has also been induced artificially by injections of œstrone.

Whether the œstrone and other cancer-inducing substances act merely as "sensitisers" of the body-cells and so render these cells liable to attack by a virus or some other directly-acting carcinogenic agent: or whether they themselves act in the latter *rôle*, is still unknown. It has been suggested that they may produce their effects upon the breast-tissue by stimulating it to precocious maturity—such mature cells being then more readily stimulated to excessive growth by some hereditary predisposing cancer-producing factor. Cancer, however, has *not* been artificially produced locally by the long-continued application of œstrone to the skin-surface itself; nor is cancer of the breast induced in strains of mice *not* naturally liable to its spontaneous occurrence; whereas the local application of the carcinogenic synthetic hydrocarbons does produce epitheliomatous transformation of the skin at the actual site of application.

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[1] J. M. Robson and A. M. Bonser, *Nature*, 1938, **142**, 836; and *Jour. Path. and Bact.*, 1940, **51**, 9.

Whether the action of the various substances used for the artificial production of cancer is direct or indirect is still unknown, both in the instance of the œstrogenic and other hormones and in that of the carcinogenic synthetic chemical substances. In the case of œstrone, it is in those tissues which normally react to its stimulation, viz., the epithelium of the breast and vagina, that tumour-growth can be stimulated.

The respective *rôles* of the **growth-stimulating hormones** of the pituitary, the thyroid, the suprarenals, and the gonads, both ovary and testis, present analogous problems in the production of hyperplasias and dysplasias in the breast and prostate and in the uterine mucosa, especially at or about the period of the menopausal involution of these organs. It is said that, in animals in which the pituitary has been removed or destroyed, the experimental neoplastic proliferation of the skin-epithelium is *not* produced by the continued application of tar or benzpyrene. This line of investigation suggests that the pituitary, and perhaps the thyroid and suprarenals, exercise some control over, or stimulation of, neoplastic as well as of normal body-tissues, but it does not appear to elucidate the ultimate nature of the process of carcinogenesis. Another curious phenomenon, perhaps allied to the production of tumours, is the occurrence, referred to on p. 289, of enormous scrotal hernias in male mice following the injection of œstrogenic hormones, stilbœstrol and certain other synthetic chemical substances.

In the human subject, the influence of ovarian and also of testicular hormones is probably responsible for the development of chronic hyperplasia in the breast and prostate respectively, and even for the production of some varieties of so-called "chronic productive mastitis," "mazoplasia" or "adenosis" (pp. 935 and 937–40: and 942 *et seq.*) and "hypertrophic prostatitis" (pp. 912–15). Believers in the **viral hypothesis** of carcinogenesis regard these various hormones and other chemical substances as **sensitising** the cells and so paving the way for the attack upon them by a hypothetical filter-passing cancer-producing virus.

Another noteworthy experimental observation is that the carcinogenic action of the œstrogens can sometimes be focussed by trauma upon certain organs or tissues, *e.g.*, the breast and the cervix uteri. Though the possibility cannot be excluded that such trauma may act by displacing actively-proliferating cells and may thus stimulate their irregular growth in abnormal situations, these experiments seem to suggest that, in the absence of œstrogens or some other growth-producing or carcinogenic factor, neoplastic development of these cells would not take place; and, moreover, its development is often multicentric, and may not infrequently also be regional.

7. Research in Experimental Embryology and the Problem of Multiple-Tumour Syndromes [1]

Until comparatively recently, no definite hypothesis could be put forward to account for the occurrence of multiple-tumour syndromes (pp. 1069, 1130 and 1135), but the application of recent work in Experimental Embryology, especially that which has been termed "**embryonic induction,**" throws considerable light upon the nature and origin of this group of **multiple neoplastic diseases.** In this connection, the experimental work of Needham, Waddington and their colleagues [2] is of special interest and value. The discovery by Hans Spemann,[3] of Wurzburg, in 1918, that there is, in the gastrula-stage of the developing embryo, an "**organisation-centre**" in the dorsal lip of the blastopore, the function of which is to stimulate the ectoderm of the embryo to give rise to the neural groove (becoming the neural canal), the notochord and the somites, was the fundamental experiment upon which this new science has been founded. It has now been shown that the ectoderm of the area pellucida must be "**competent**" to react to this stimulus, and that the experimental implantation, say in the flank of the developing embryo, of a fragment of tissue containing living cells from this evocator-centre, can induce or evoke the development of a secondary or "parasitic" neural axis (*cf.* Figs. 129 and 130, p. 292). Not only so, but a similar development can be induced by implanting the cells previously killed by boiling, or even by the use of an ethereal extract of them, the chemical substance involved being apparently of the nature of a **sterol,** *i.e.*, a member of the chemical group which includes the anti-rachitic vitamins, the male and female sex-hormones, as well as œstrogenic, carcinogenic and other important stimulating or activating substances. Not only can the development of normal structures, organs and tissues be evoked in their normal sites, but their development can also be brought about in abnormal positions, *e.g.*, an ear-drum in the flank, by the use in that position of an implanted fragment of cartilage. Even by the use of extracts, not only of embryonic, but of adult, tissues containing the needful sterol-like compounds (these may require to be themselves "activated" by the addition of nucleic, oleic, or other higher fatty acid) such abnormal developments can be artificially induced—and it is but a step further to produce, not normal, but **pathological, forms of growth.**

In the frog it has been proved that "over-ripeness" of the ova, *i.e.*, if they are kept for a longer period than usual before they are fertilised, will cause many of them to give rise to the production of double monsters, or, if kept longer still, to teratomatous tumours, which may be actively proliferative and often definitely malignant in character. This over-ripeness involves a disturbance of the metabolism of the **sterols,** and the development of secondary or parasitic embryos may be induced in the flanks or belly of the primary embryo just as they were by experimental implantation of evocator substances.

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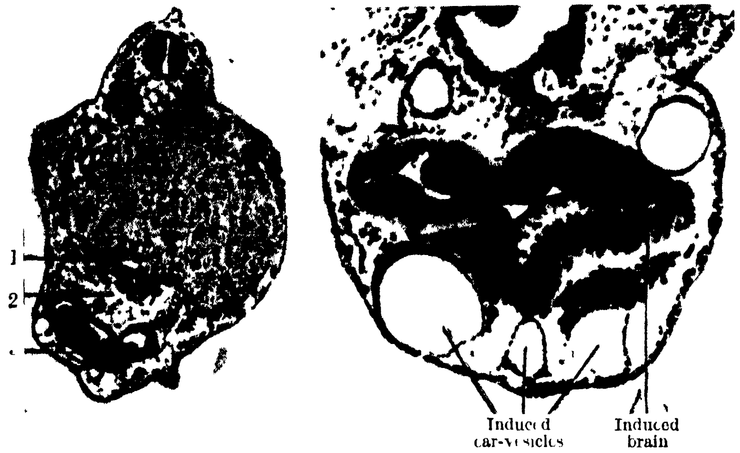
[1] This section is adapted from an article upon "Multiple Meningeal and Perineural Tumours with Analogous Changes in the Glia and Ependyma (Neurofibroblastomatosis)," by Worster-Drought, Carnegie Dickson and McMenemey, in *Brain,* 1937, **60,** 85–117, in which full details and references are given. For the derivation of the word "syndrome," *see* second footnote on p. 1069.

[2] J. Needham, "New Advances in the Chemistry and Biology of Organised Growth," *Proceedings of the Royal Society of Medicine,* London, 1936, **29,** 1577; J. Needham, C. H. Waddington, and D. M. Needham, "Physico-Chemical Experiments on the Amphibian Organiser," *ibid.,* 1934, **27,** 393. See also Arthur Keith's "Human Embryology and Morphology," 5th ed., 1933, Chap. IV., p. 52 *et seq.* C. H. Waddington, "Experiments on Embryonic Induction," *Journal of Experimental Biology,* 1934, **11,** 211.

[3] Hans Spemann, "Embryonic Development and Induction" (English Translation), Yale and Oxford University Presses, 1938.

Over-ripeness evidently acts in the same way as boiling, and liberates these substances indiscriminately. Under this stimulation, the ectoderm may become thickened and undergo epitheliomatous development. In embryos in which the cerebral vesicles have already appeared, there may be various disturbances of "second-grade induction," leading to deficiencies or malformations or to the production of tumour-like masses.

Needham points out that, with ova which under optimum conditions would produce, say, 90 per cent. males, the first effects of "over-ripeness" are deviations in the sex-hormones: next, the uncontrolled liberation of the evocators and the production of monsters or terata, and lastly the production of a carcinogenic agent and the development of teratomata—tumours in which malignancy in varying degree may supervene, the cells escaping, as it were, from the control of the "individuation field" and running wild as epithelioma or sarcoma. The production of teratoid and teratomatous tumours may be explained in Needham's phrase by "the possible permutations and combinations of irresponsible organisers and perversely competent tissues"; and he states it as his belief that "all further progress in unravelling these phenomena will depend upon our knowledge of the sterols."



A. FIG. 129. B.

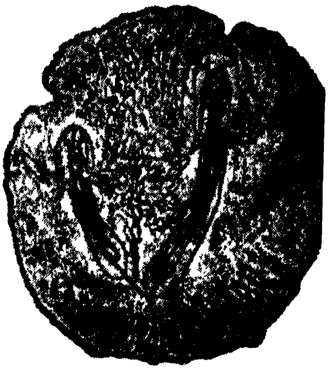


FIG 130.

FIG. 129. (A) *Experimental induction of a secondary embryo or "Siamese twin" in amphibian (newt) embryo by implantation ventrally of a fragment of boiled mouse-heart* Normal neural canal of "host" embryo, with notochord below it, seen centrally at upper (dorsal) part of figure 1, secondary gut: 2, implanted mouse-heart: 3, induced brain × 35 (approx).

(B) *Chaotic induction by implantation of boiled mouse-liver in a newt-embryo secondary brain and five ear vesicles* and (at middle of upper margin of photograph) a secondary lumen in the entoderm (after Holtfreter). × 60 (approx.).

FIG. 130. *Twinning of chick-embryo by production of two primitive streaks upon one blastoderm,* probably owing to controlled liberation of "primary evocator" at two separate points on blastoderm (after Tannreuther). *Cf.* Fig. 192, p. 357.

(By courtesy of Dr. Joseph Needham, F.R.S.)

For the three annexed illustrations, from articles by Holtfreter and Tannreuther, we are indebted to the kindness of Dr. Joseph Needham, F.R.S., who explains [1] that the first of these, a transverse section through an amphibian embryo, shows at its upper (dorsal) part the normal developing neural canal and notochord (compare Fig. 192 in the Appendix, p. 357) of the host ; whilst below (ventrally) the development of a secondary or " Siamese-twin " embryo has been induced by the implantation of a fragment of mouse's heart into the blastocœle-cavity. Above the implant (the pale area), is seen the commencing development of the gut of this " induced twin " ; whilst below, between the implant and the ventral surface of the host, is a large brain-like neural structure which may be compared with the normal neural canal of the host at the top of the figure. Dr. Needham's note on the second of these illustrations (B) is that it " shows a chaotic induction, with no less than five induced ear-vesicles visible in this one section. Only the secondary (induced) embryo is seen, that of the host itself being one is out of the picture, above."

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[1] **In a personal communication of 31st March, 1939, he adds: "It seems to me that organiser phenomena and cancer are connected for the following three reasons: (1) Cancer must surely be regarded as an escape from that individuation-field which by its strength causes the power of regeneration seen in some animals, and, by its weakness, the absence of this power in others. (2) Synthetic carcinogenic substances are definitely among those which perform neural inductions in the embryo, and it has just been proved that one of them, 1:2:5:6-dibenzanthracene α-β endo-succinate, acts as an inductor in amounts so low as to be of the order of the amounts in**

8. Therapeutic Work in Relation to the Pathology of Malignant Disease

As experimental cancer-research is greatly limited by the difficulties attending any attempt to investigate *human* forms of the disease, certain observations which have resulted from attempts to eradicate or limit malignant growths in man are of considerable interest and value in studying the pathology of malignant disease in general.

Apart from complete surgical removal, irradiation by radium and deep X-rays hold the most important place in the therapeusis of malignant disease. Both of these forms of irradiation bring about destruction of cells, but this destructive action is much greater in the case of proliferating cells, *i.e.*, during their mitotic division, than in those which, like the mature cells of the adult body, are relatively quiescent as regards proliferative activity. The destructive action of radium and deep X-rays on the cells of malignant growths was investigated by Canti and Donaldson, who studied cases of carcinoma of the cervix uteri. By removing small fragments of the tumours at different stages of treatment by irradiation, these workers were able to show by histological methods that the changes induced were, firstly, a cessation of mitosis : later, abnormal mitosis of a type suggesting the action of dying cells : and then the actual necrosis of the tissue irradiated. Later, the irradiated mass of tissue showed signs of inflammatory reaction, with migration of leucocytes into the necrosed area, and finally a process of fibrosis (Fig. 666, p. 1088).

In his later work with tissue-cultures of malignant cells, Canti showed by his ingenious methods in " speeded-up " cinematographic films that these cells appeared literally to shrivel up under the action of irradiation by X-rays or radium.

Apart from the employment of radium and X-rays, there remains for consideration the work done on the treatment of malignant disease by injection of certain chemical compounds of the heavy metals, particularly lead. Such compounds of lead bring about necrosis of chorionic tissue, and their action in producing abortion is well known. As chorionic tissue has proliferative and invasive characters not unlike those of a malignant tissue, it was supposed that

which vitamins and hormones work. (3) There is a parallel between cancer and homoiogenetic [or autogenous] induction." . . . " I fully believe that all the teratoma phenomena can be explained on the basis of organisers in places where they should not be, and competences to react to them being prolonged after they ought to have ceased. . . . H. J. Bagg, in the *American Journal of Cancer*, has produced teratomata experimentally in the adult fowl by injections of zinc salts into the testis. Moreover, in a recent number of the *Collecting Net* (Wood's Hole Marine Biological Station), Schotte claims to have induced teratomata by implanting pieces of mouse-embryo tissues into a mouse-fibrosarcoma."

lead-compounds would have a destructive action on malignant cells, producing a necrosis which might be expected to heal subsequently by fibrosis. In practice, the therapeutic use of lead has often been followed by a process of necrosis in a malignant tumour, but the results of treatment are by no means as constant as are those following the use of radium or X-rays. The exact method of action of lead on malignant cells remains in doubt, but it seems likely that lead-compounds are taken up by cells of the reticulo-endothelial system and that the amount of lead determined to any particular tissue of the body depends on the richness of that tissue in reticulo-endothelial cells. In the case of tumours, the presence of reticulo-endothelial tissue is not a characteristic feature, and hence, as might be supposed, the amount of lead found in a malignant tumour after treatment of a patient with lead-compounds is frequently less than that found in normal tissues such as those of the liver or spleen. It has been suggested that the lead-compounds act by damaging the endothelial lining of small vessels and thus cause thrombosis, which, by impairment of the blood-supply to the tumour, results in necrosis. Another suggestion is that the presence of the absorbed lead in tumour-cells renders them more sensitive to the destructive action of the irradiation, and that, if employed, the two methods of treatment should therefore be combined.

GENERAL CONCLUSIONS REGARDING THE ÆTIOLOGY OF TUMOURS

We thus have, as yet, no accurate information as to the ultimate causation of new growths, but it is probable that all tumours are *not* necessarily due to the same cause, and one or more of the above ætiological factors may play a part in the causation of any individual new growth. Some morbid conditions now classed as tumours will, in all likelihood, be found to be due to as yet undetected animal or vegetable parasites, including viruses. Some are certainly produced by special and prolonged kinds of irritation, though this may only predispose the tissues to invasion by a special organism, or, as stated on p. 289, bring into action some growth-producing factor present normally in "tumour-susceptible" subjects. Some tumours, again, have been thought to be due to the inclusion of " blighted " or aborted ova or their products, *e.g.*, teratomatous dermoids ; but the part played by germ-cells in the production of tumours is still problematical. According to the views held by Needham, Waddington and others based upon the results of experimental embryological research, to which reference is made on p. 291, monsters and teratomatous tumours may be explained on the basis of a stimulation by specific substances of some part of the developing embryo which is still competent to develop in a given direction or in which abnormal " evocating " substances have been freed. Intermingling of tissues, developmentally or otherwise, also appears to be a well-established cause, though it may be only a predisposing one. Anaplasia or reversion to primitive or embryonic tissue, though it suggests the possible **mechanism** of the process, gives us no **explanation** as to its direct cause—in fact it describes the " *how*," but not the " *why*," of tumour-formation.[1]

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[1] The Chevalier Jacksons, father and son, in their book, " The Larynx and its Diseases," (W. B. Saunders Company, Philadelphia and London, 1937, p. 378), writing of the causation of laryngeal cancer, suggest an ingenious " algebraic formula "—which can be modified or extended indefinitely according to the site of the lesion and the views of individual observers—as follows :—

$$A + S + C + I + F + a + T + X\ Y\ Z = Æ$$

in which A equal age : S, sex : C, senile changes in the epithelium, including increased vulnerability to " cancer " : I, irritation : F, frustrated repair : a, alcohol : T, tobacco-smoke : X Y Z, the as yet undetermined factors : and Æ, the ætiology.

THE RELATIVE DIFFERENCES BETWEEN SIMPLE AND MALIGNANT TUMOURS

As has already been emphasised, these differences are a matter of degree only; and, in certain cases, lying on the borderland between the two great groups, it is sometimes very difficult or even impossible, from histological examination alone, to determine whether a given tumour is or is not malignant. This difficulty, well recognised by every pathologist, cannot be too strongly emphasised; and, for the diagnosis and prognosis of such cases, the microscopical and naked-eye characters of the tumour, the site of origin, the rapidity of growth, and the known proclivities of similar tumours growing under similar conditions, the age and sex of the patient, and other clinical data must be carefully considered, and also whether the tumour has or has not been submitted to any form of irradiation-treatment. In every such case, therefore, **the pathologist must have at his disposal all relevant information,** when he is asked to determine the degree of malignancy of individual tumours, or of tissues suspected to be neoplastic in their nature. The more important points to be kept in mind in this connection may be summarised as follows.

The site of origin and the known proclivities of similar growths in other previously observed cases. In some situations in the body, the likelihood that a given tumour is malignant may be determined partly by such factors as the extent of the vascular supply, or the exposure of the part to irritation, *e.g.*, in the case of the gall-bladder the presence of gall-stones, or in that of the tongue or lips the presence of a jagged tooth. Organs subject to involution and analogous processes, for example the breast and uterus or the prostate, are specially liable to become the site of malignant tumours.

Some malignant adenomas of the sigmoid flexure or rectum may have little tendency to cause distant secondary growths, whereas other apparently precisely similar tumours growing from the stomach may increase rapidly and give rise to numerous metastases. A slow-growing bronchial carcinoma may in the same way suddenly become the source of multiple rapidly-growing metastases in the brain and elsewhere. Most gliomas, even the rapidly infiltrating glioblastoma multiforme, rarely cause secondary growths. A slow-growing tumour of the stomach may, when it reaches and invades the liver, grow much more rapidly, take on a softer form of growth, and become highly malignant. Some round-celled sarcomas are, when growing from bone, only slightly malignant, but, when growing from connective tissue, *e.g.*, in subcutaneous tissue, may be highly so. Secondary growths from cystadenomas of the ovary are rare, even though these tumours are very complex in structure, but they may occur, *e.g.*, in the peritoneum. Though giant-celled tumours of bone—formerly termed " myeloid sarcomas "—can and often do invade the neighbouring tissues, particularly the bone-marrow itself, they may not give rise to metastases; but it is important to recognise that this is *not* invariably the case, and, as pointed out on p. 309, secondary growths do occasionally occur in the lungs, especially after any incomplete surgical or other interference with the primary growth in the bone.

The rapidity of growth is also a valuable guide; and, although some malignant neoplasms (*e.g.*, scirrhous cancers) are extremely slow in their development, yet, if a tumour grows rapidly and is highly cellular, and if there is rapid and perhaps aberrant mitotic division and production of cells, the evidence is in favour of a diagnosis of malignancy (Figs. 127–8, p. 276).

Naked-eye Examination. The shape, consistence, and general appearance of a tumour often give valuable information; and the presence or absence of hæmorrhage, necrosis, umbilication or ulceration, as well as any naked-eye evidence of infiltration and of metastasis, should be noted. In some instances, the information so obtained may appear to be completely negative in character, and yet the tumour may ultimately prove to be malignant; for example, it may be impossible, in some cases, by naked-eye examination alone, and sometimes even on microscopical investigation, to distinguish between "simple" chronic glandular hyperplasia (pp. 920–1) and early diffuse malignant adenoma of the endometrium—the one condition, histologically at all events, gradually merging into the other—a problem often equally difficult in the case of chronic fibroid conditions of the breast when accompanied by proliferative changes in the glandular epithelium (p. 344 *et seq.* and p. 937 *et seq.*).

Microscopical Examination. In "**simple tumours,**" there is usually considerable regularity and a definite character in their structure, which resembles more or less approximately that of a mature, "adult" or fully-developed tissue. There is absence of infiltration at the margin, and there is usually, though not always, definite encapsulation of the growth by fibrous tissue derived from the surrounding structures; and, in some of the simple adenomas, each glandular acinus has a definite basement-membrane. This "capsule" is sometimes entirely absent, *e.g.*, in certain chondromas and angiomas. If simple tumours are multiple, as in the case of multiple lipomas, uterine myomas, neurofibromas, etc., they are usually all primary, *i.e.*, are not due to the occurrence of metastasis, and this is true also of the tumours found in many of the other so-called multiple-tumour syndromes (pp. 1130 and 1135).

In "**malignant tumours,**" the histological structure is, as a rule, grossly irregular, and there are usually definite, and sometimes marked, aberrations in general structure, size, shape, and type of cell (*e.g.*, the so-called anaplastic tendency already described), this tendency towards such aberrations being very much more pronounced than in simple tumours. Yet it may, without other information, be impossible, in certain individual instances, to distinguish the cells of some mixed- and spindle-celled sarcomas from those of granulation-tissue, or the cells of an extremely malignant lymphosarcoma from those of normal or of hyperplastic lymphoid tissue; and, similarly, the pigmented cells of a malignant melanoma and of an ordinary simple pigmented mole closely resemble each other in general character and arrangement. Moreover, the variations often present in different parts of the same tumour must be borne in mind when selecting portions for microscopical examination. The occurrence of **infiltration** at the margin of the growth is extremely important, and hence **the tissue at the junction of a representative portion of the tumour and sufficient of the surrounding or subjacent tissues should always be carefully investigated.** Some tumours which may have little tendency to produce metastatic growths elsewhere may, nevertheless, exhibit marked **local malignancy,** and rapidly infiltrate and destroy the surrounding tissues, as in the case of some gliomas, the majority of myelomas, and the papillo-adenoma or villous tumour of the uterus of elderly women—hence the tendency of some writers to regard the occurrence of metastases as a necessary criterion of malignancy is to be deprecated. Again, some malignant tumours may appear to be surrounded by a definite fibrous-tissue capsule, and yet give rise to extensive secondary growths.

The structural characters of the blood-vessels are often of great importance, for example in the case of sarcomas ; but even here it is sometimes difficult or perhaps impossible to distinguish, say, the primitive characters of the vessels of some sarcomas from those of the simple granulation-tissue seen in repair, or in some of the infective granulomatous diseases.

THE NOMENCLATURE AND CLASSIFICATION OF TUMOURS

A scientific classification of tumours is, admittedly, difficult or even impossible in the present state of our knowledge, chiefly because the ætiology of tumour-formation is still uncertain. Of the several classifications put forward in the past, that of Adami is at once the most complete, logical and satisfactory from the scientific point of view. The introduction of many new terms has, however, militated against its general adoption. Careful examination of the position reveals but two courses open for use in a Textbook of Pathology : that of adopting some such classification as Adami's (either as a whole or in simplified form) : or of following the custom of giving a mere heterogeneous catalogue of varieties of tumours. We propose, therefore, to adopt a modified form of the Adami classification, omitting some of the terms originally suggested, believing that it will prove more useful to the student than an unclassified list of tumours.

For the convenience of those who would pursue the Adami classification farther, the entire system originally suggested has been set out fully in Appendix II, on page 355, at the end of our next chapter.

Two main divisions of tumours are first recognised :—

A. Those derived from the growth of cells and tissues of the individual in whom they are developed (the " Blastomata " of Adami).

B. Those derived from the growth of cells and tissues of one individual within the tissues of another individual of the same species (the " Teratomata " of Adami).

The first group, A., is farther divided into :—

I. " Pulp-tumours " : *i.e.*, those arising from the supporting or connective tissues.

II. " Rind-tumours " : *i.e.*, those which arise from tissues forming covering- and lining-membranes (including the epithelial cells of glandular organs).

In each instance, simple or malignant tumours may be formed either from the pulp-series or from the rind-series, so that ultimately there are four subgroups in this first Group A (*see* Table on p. 299).

NOTE.—The suffix **-oma** is derived from the Greek word *ὤμος*, *ōmos*, meaning raw, uncooked—used especially of flesh (hence the word " omotherapy " for treatment with a raw-meat diet). Galen used the term *σάρκωμα*, *sarcōma*, for " a fleshy excrescence, especially in the nose " (Liddell and Scott). It then became the generic and technical termination of any word signifying a neoplastic growth or tumour. We apologise to our classically-minded readers for adopting the Anglicised plural in " -s " in place of the more correct and euphonious Greek forms such as " sarcomata " or " carcinomata."

CHAPTER XIII

SPECIAL VARIETIES OF TUMOURS

In many instances the descriptions of typical and atypical tumours derived from the same species of tissue to a certain extent overlap, and, though in some respects it might be more scientific to group simple and malignant analogues (for example, the simple and malignant adenomas) together, we propose to describe the special varieties of tumour under the headings set out in the table opposite. In this connection, see also the important note on the "Reticuloses and Reticulo-Endothelioses" on p. 1262.

A. BODY-TISSUE TUMOURS (BLASTOMAS) [1]

I. PULP-TUMOURS

(i) SIMPLE or TYPICAL (SIMPLE CONNECTIVE-TISSUE SERIES)

1. **FIBROMA.** In histological structure, fibromas closely resemble normal fibrous tissue. They vary in consistence, not only in the case of different

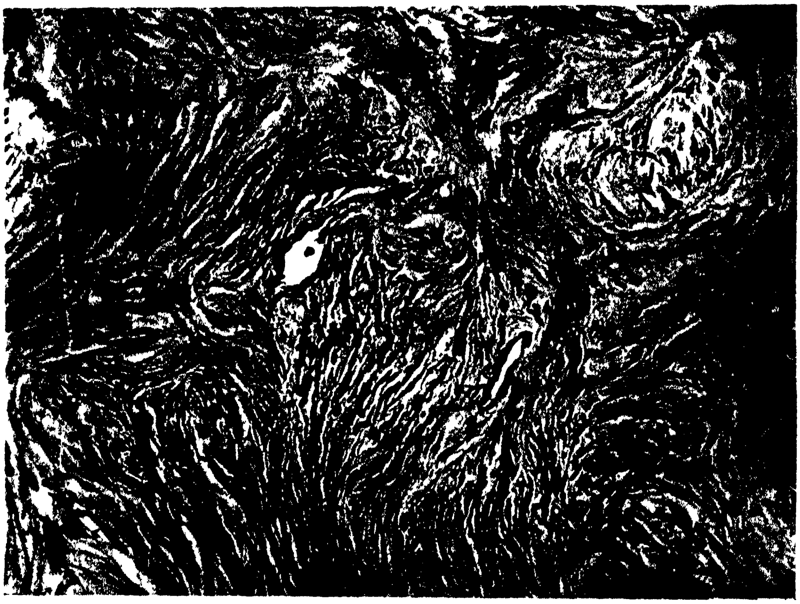

FIG. 131. *Hard Fibroma*, composed of dense, fully-formed fibrous tissue. × 200.

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[1] The term "Body-tissue tumour" is here taken to mean a tumour arising in tissues belonging to the body-plan or individuation-field of the *original* individual, and the term "Extra-body-tissue tumour" as signifying one formed outside the body-plan or individuation-field of the *original* individual; though in the latter case the tumour *may be induced* in the still competent tissues of the same individual. The recent work of Waddington, Needham and others (referred to on p. 291) on Experimental Inductive Embryology suggests that certain types of tumours previously regarded as "congenital," *i.e.*, the teratomas and teratoid tumours, may be due to the action of chemical substances, allied or belonging to the sterol-group, which normally act as "evocators" of the development of tissues and organs; and, abnormally, may lead to the development of secondary or induced reduplication of structures or to the production of tumour-growths in the body of the embryo.

TABULAR LIST
OF
SPECIAL VARIETIES OF TUMOURS

A. BODY-TISSUE TUMOURS (Blastomas)

I. PULP-TUMOURS :—

(i) **Simple or typical** (simple connective-tissue series)

1. Fibroma (p. 298).
2. Myxoma (p. 301).
3. Lipoma (p. 303).
4. Chondroma (p. 303).
5. Chordoma (p. 306).
6. Osteoma (p. 306).
7. Odontoma (p. 308).
8. Osteoclastoma (p. 308).
9. Lymphoma (p. 311).
10. Myoma (p. 313).
11. Glioma (pp. 315 and 1097).
12. Neuroma (Neurocytoma) (pp. 315, 1114 and 1139).

(ii) **Malignant or atypical** (malignant connective-tissue series)
Three differing groups of tumours are included here :—

(*a*) The malignant analogues of the foregoing simple tumours, and tumours of corresponding origin (the sarcomas, etc., p. 316).

(*b*) Tumours derived from meso-, endo-, and peri-thelial tissues where there is reversion to " pulp-like " characteristics (p. 321).

(*c*) The melanomas or pigmented tumours (of doubtful origin) (p. 323).

II. RIND-TUMOURS :—

(derived from " covering- " or " lining-tissues ")

(i) **Simple or typical**

(a) **Epithelial**
Adenoma (p. 325).
Papilloma (p. 328).

(b) **Endothelial**
Hæmangioma (p. 331).
Lymphangioma (p. 332).

(ii) **Malignant or atypical**
Here are included ·—

(*a*) The malignant analogues of the foregoing simple epithelial rind-tumours—the " cancers " or carcinomas (p. 334).

(*b*) The malignant meso-, endo-, and peri-theliomas in which " rind " characters persist (p. 321).

B. EXTRA-BODY-TISSUE TUMOURS [1] or TERATOMAS

(including placentomas and teratoid tumours) (p. 351).

These tumours have hitherto been regarded as composed of the products of the " germ-cells " included within the tissues of an individual of the same species.

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[1] *See* footnote on p. 298.

individual tumours, but frequently also in different parts of the same tumour. **Hard fibromas** are usually slow-growing, and are composed of dense fibrous tissue with few cells and numerous fibrils of collagen. **Soft fibromas,** on the other hand, are more cellular and less fibrillar, and tend to grow more rapidly. All intermediate gradations between these two types of fibroma and between the softer varieties of fibroma, through the fibro-sarcomas to the sarcomas, occur. The blood-vessels of fibromas may be well-supported and possess definite walls, but they are not infrequently imperfectly-formed, the muscular coat in particular being often deficient. The vessels may, in some cases, be represented merely by thin-walled, dilated spaces lined by endothelium.

The majority of fibromas are definitely encapsulated, and this is especially the case when the tumour is growing within a solid organ. When a fibroma grows in the wall of a hollow viscus it commonly becomes pedunculated, giving rise to a so-called "polypus." Even then, evidence of encapsulation is seen in the form of the covering present on its free surface, as this is derived from the organ in which the growth has occurred. This investing tissue, in certain cases, becomes ulcerated and in varying degree may disappear. Evidence of such happening is to be found in the inflammatory reaction which is observed near the surface of some pedunculated fibromas.

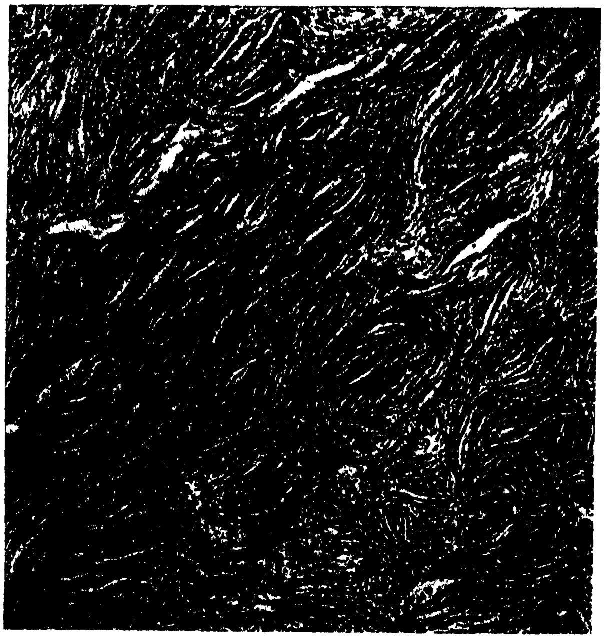

FIG. 132. *Soft Fibroma,* showing young fibrous tissue arranged in irregular bundles. × 75.

Chronic inflammatory thickenings composed of fibrous tissue, *e.g.*, the chronic irritative overgrowths often seen in the capsules of certain organs such as the spleen or liver, or on the pleural surface of the lung, and chronic inflammatory lesions in glandular organs, *e.g.*, chronic mastitis, often closely resemble fibromas or fibro-adenomas, and are often difficult to distinguish from true tumour-formations.

Sites. Fibromas may arise from connective tissue in any position, but are found especially in the skin and subcutaneous tissue, fasciæ, and fibrous tissues such as the dura-mater, periosteum, fibrous sèpta, tendons, nerve-trunks, cicatricial tissue, and in the stroma of some glandular organs, *e.g.*, the kidney (in which the tumours are situated most frequently in the pyramids), uterus, ovary or breast.

Degenerations and **metaplastic changes** are common, and all varieties intermediate between other members of the "pulp-tissue" tumours of the same series may be found, especially fibro-myxomas, fibro-myomas and fibro-sarcomas.

Neurofibromatosis, when affecting the fibrous-tissue sheaths of cutaneous nerves (von Recklinghausen's disease), is a peculiar tumour-like process, sometimes described as **molluscum fibrosum,** the nodules varying in size from that of a pin's head or a pea up to several inches in diameter. These may affect the distribution of a single, or more usually of many, cutaneous nerves, and they may be present in some cases in enormous numbers. They may gradually push aside or even invade the surrounding tissues, and may also develop from the deeper nerves. Neurofibromatosis is one variety of "multiple-tumour syndrome" and the neurofibromas on the subcutaneous and other peripheral nerves may be associated with analogous tumours on the cranial nerves and spinal nerve-roots (central neurofibromatosis), meningiomas, gliomas and other anomalies. A further description of this disorder will be found on p. 1135.

Plexiform "neuroma" (or, more accurately, **neurofibroma**—p. 1139), is an analogous change affecting certain nerves, especially those of the head and neck, in which the neurofibromatosis is diffuse, rather than nodular as in von Recklinghausen's disease. The affected nerves become thickened, elongated and tortuous, with diffuse fibromatous overgrowth. For a description of **neurolemmomas,** see pp. 1141–3.

Cheloid[1] is a condition characterised by excessive reparative processes, and consists of a fibrous overgrowth in the subcutaneous tissues. The new tissue is often considerable in amount and suggests a tumour composed of dense fibrous tissue. Cheloid is seen sometimes as a sequel of burns (p. 185). Histologically, the tissue-mass is composed almost entirely of collagen-fibrils with scanty fibroblasts, mostly in the peripheral parts of the growths. The negro exhibits a marked propensity to the development of cheloid.

2. **MYXOMA.**[2] A tumour composed of "mucinoid" or "myxomatous" tissue, similar in character to the tissue which, in the fœtus, precedes the other connective tissues, and which persists in the umbilical cord as the so-called "Whartonian jelly." Such tumours are soft, jelly-like and translucent, and present great variations in their microscopical appearances. They consist of rounded or irregular, or frequently triangular or stellate, cells with branching processes forming a delicate interlacing network, in the meshes of which there is a clear homogeneous, or granular, or sometimes finely-fibrillated, intercellular material, containing a large proportion of mucin or some mucinoid substance (Fig. 133, p. 302).

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[1] See footnote on p. 268 *re* spelling of this word.

[2] We employ these terms "myxoma" and "myxomatous" here as referring to a tumour derived from, or developing into, a *slimy* or "*mucoid*" or "*mucinoid*" *tissue* like that of the loose-textured jelly-like mesenchymatous connective tissues of the embryo or fœtus. The word "mucus" is derived from *μύκης*, *mŭkēs*, *gen.* *μύκητος*, *mukētos*, a slimy moist fungus. *Μύξα*, *muxa*, is the slimy discharge from the nose, and *μυξώδης*, *muxōdēs*, means like mucus, slimy or pulpy. All of these terms, therefore, refer to the slimy or pulpy nature of the tissue or tumour, and need not necessarily imply the presence of "mucin," the albuminoid constituent of "mucus," discovered and named long after these other words were originally invented as medical terms.

True myxomas are rare tumours, and the majority of those so described probably represent examples of fibromas, lipomas or chondromas which have undergone various degrees of mucinoid degeneration, a condition which may also be found in glandular tumours, *e.g.*, in the so-called " colloid " cancers, myxo-adenomas, etc. Nevertheless, pure myxomas sometimes occur in the subcutaneous or submucous tissues, in nerve-sheaths, in the retroperitoneal connective tissues and elsewhere. The " hydatidiform mole," found occasionally in the uterus in place of the normal products of conception (Fig. 191, p. 352, and *cf.* Figs. 550–1, p. 925), is by some authorities regarded as a myxomatous degeneration of the chorionic villi, but is rather to be regarded as a chorionepithelioma simplex, *i.e.*, the simple tumour which corresponds to chorionepithelioma malignum (p. 352, and Figs. 552 and 535–6, pp. 926 and 910). Many so-called " mucous polypi," growing from the nasal, uterine or intestinal mucous membranes, are in reality chronic inflammatory overgrowths and not of the nature of true tumours; and their polypoidal character results from the traction exercised upon them by the contents passing along these channels. Mucinoid degeneration, occurring in inflammatory and other tissues, should also be differentiated from true tumour-formation.

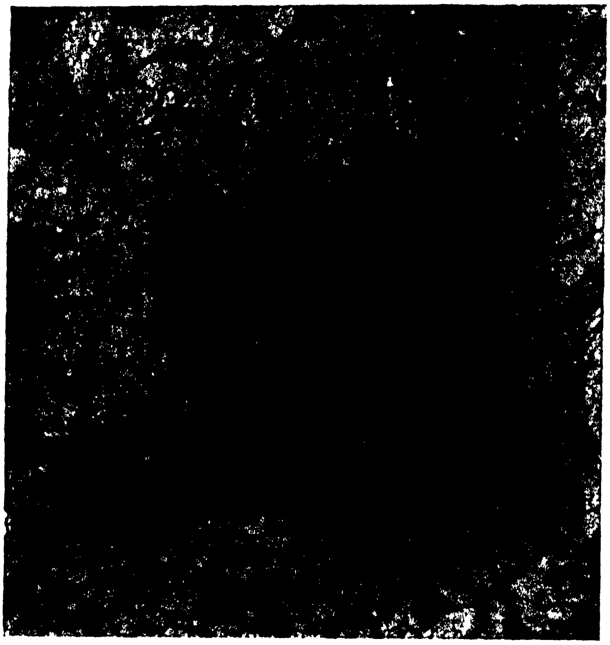


FIG. 133. *Myxoma of Breast*, showing the characteristic branching cells. The walls of the blood-vessel, seen in section, are deficient in muscular fibres, and are somewhat cellular, there being a condensation of tumour-cells immediately around it, forming a supporting adventitial layer. × 250.

Though usually simple tumours, myxomas are sometimes diffuse and may spread widely. They seldom give rise to secondary growths; and, when these occur, it is probable that the primary tumour is in reality some malignant neoplasm which has undergone mucinoid degeneration. It may also be noted here that cysts containing mucin are of common occurrence in tumours derived from the cells of mucous membranes and in metastases from these when malignant (pp. 349–350). A fairly common site for the development of a myxoma is the fascia of the thigh, particularly in the popliteal space. In this region, myxomas are seldom encapsulated, and attempts at local removal are frequently followed by " recurrence." The prognosis in the case of patients with myxoma must be more guarded than with the majority of the "simple" supporting-tissue tumours, as recurrences are often definitely sarcomatous.

3. **LIPOMA.** Except that, to the naked eye, they are usually rather paler in colour, these tumours macro- and micro-scopically resemble ordinary adipose tissue in their structure (Fig. 134), differing in some instances only in that there is a coarser pattern of both cells and lobules. They are probably the most innocent and chronic variety of tumour-growth known. They are frequently multiple, and grow from the subcutaneous tissue, especially about the neck, shoulder, back, or buttock : from the extra-peritoneal fatty tissue, omentum, or appendices epiploicæ : or in certain of the viscera. They are found occasionally in or between muscles, in the periosteum of bone, and in synovial membranes. Lipomas are often very slow-growing, and occasionally attain a large size. They are usually surrounded by a delicate fibrous capsule, which sends in septa between the lobules of the tumour. They sometimes appear early in life. Transitions between lipomas and myxomatous and fibrous tumours are common. Tumours consisting of fatty tissue mixed with some other connective-tissue element are common, *e.g.*, fibro-lipoma, myxo-lipoma, angio-lipoma. Congenital lipomatous tumours of the meninges (Fig. 678, p. 1096) are very rare.

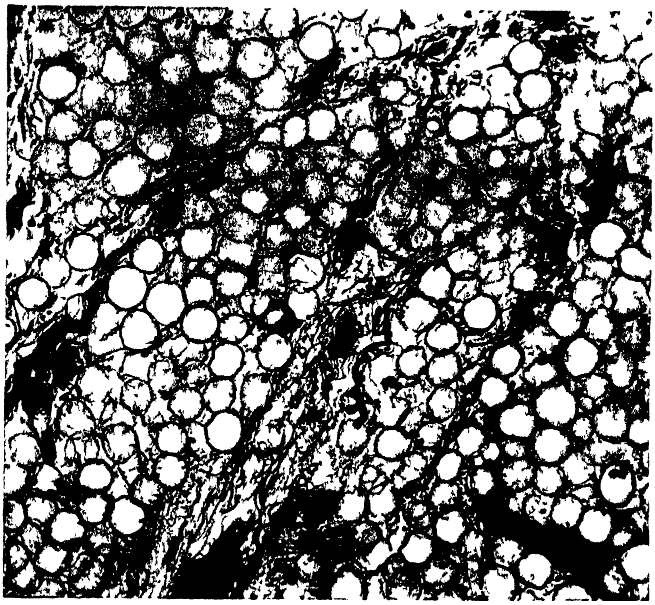


FIG. 134. *Lipoma*, showing structure closely resembling that of ordinary adipose tissue. × 60.

As well as the sharply circumscribed lipomas just described, more diffuse formation of fat or **lipomatosis**—distinct from normal subcutaneous fat, occurs, and is, for example, seen as the " diffuse lipoma " of the neck ; whilst adiposis dolorosa (Dercum's disease) is a non-neoplastic dystrophy of the subcutaneous tissue.

4. **CHONDROMA** (*see also* p. 1225). These tumours, composed of cartilage, form a somewhat variable series, and frequently exhibit metaplastic changes. They grow most commonly in connection with the bony skeleton, *e.g.*, from the ends of long bones such as the humerus (Fig. 135, p. 304)—only rarely from

pre-existing normal cartilage—and are formed most frequently in the substance of the bone, or under the periosteum. They are said to occur more especially after rickets, and may be due to new growth supervening in islets or groups of cells, derived perhaps from epiphyseal or other cartilages which have become isolated and enclosed in the growing bone during the abnormal processes of ossification occurring in that disease. In such cases they are often multiple, and grow especially from the bones of the hands and feet (Fig. 136).

Chondromas often undergo varying degrees of calcification or imperfect ossification; and exostoses are frequently developed as cartilaginous tumours, which become ossified later, the ossification occurring in the central part, and the surface being occupied by a layer of proliferating cartilage. Such tumours are usually composed of rounded or irregular islets of translucent or semi-translucent, white or bluish-white hyaline cartilage, separated and surrounded by a framework of connective tissue containing the nutrient blood-vessels and acting as a formative perichondrium (Figs. 137 and 138). A gradual transition between this connective tissue and the fully-formed cartilage in the interior can usually be traced. The cartilage-cells, especially towards the central parts of the islets, frequently show degenerative changes, irregularity in size and shape, myxomatous transformation, etc.; whilst the matrix may stain faintly and show fibrillation in these central areas. This "myxomatous" or

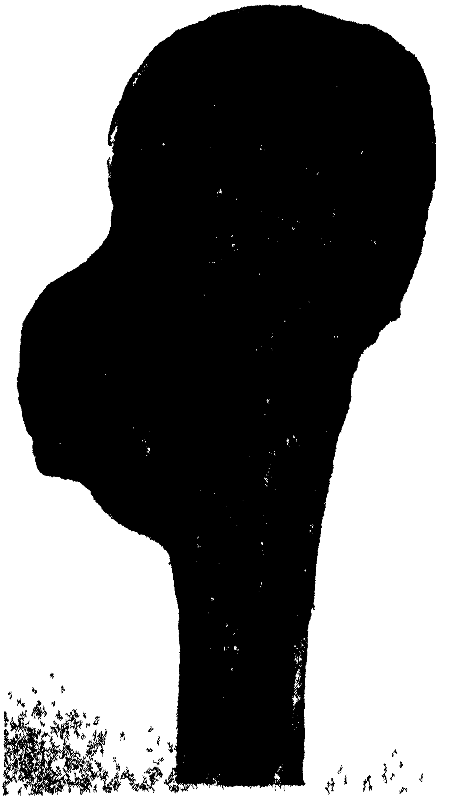


FIG. 135. *Chondroma of head of humerus*, with scattered small areas of ossification.

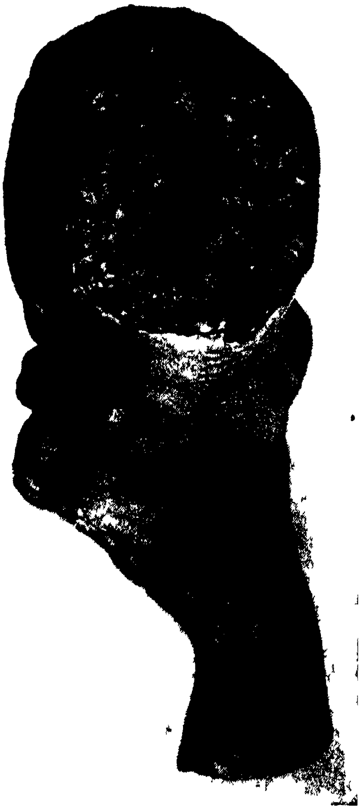


FIG. 136. *Chondroma* growing from bones of hand.

mucinoid change may lead to softening so pronounced as to give rise to cavities in the so-called " cystic " varieties of chondroma. Forms intermediate between

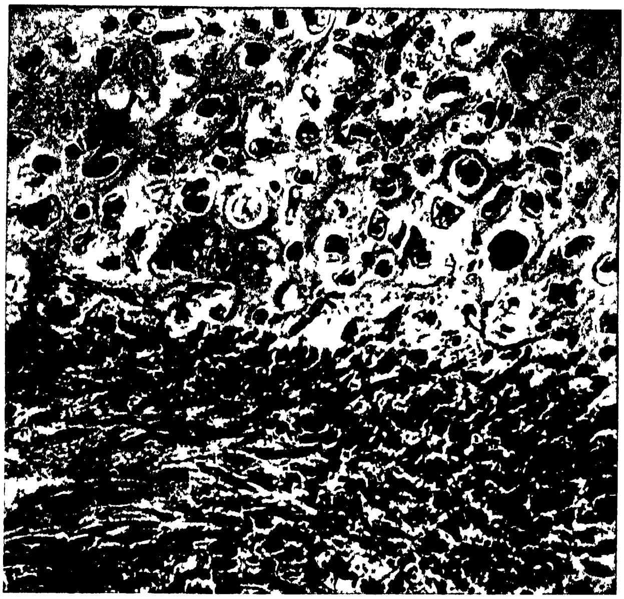


FIG. 137. *Chondroma,* showing irregular formation of hyaline cartilage. The darker tissue below is the fibrous framework of the tumour, which also acts as a perichondrium. Hæmatoxylin and eosin. × 200.

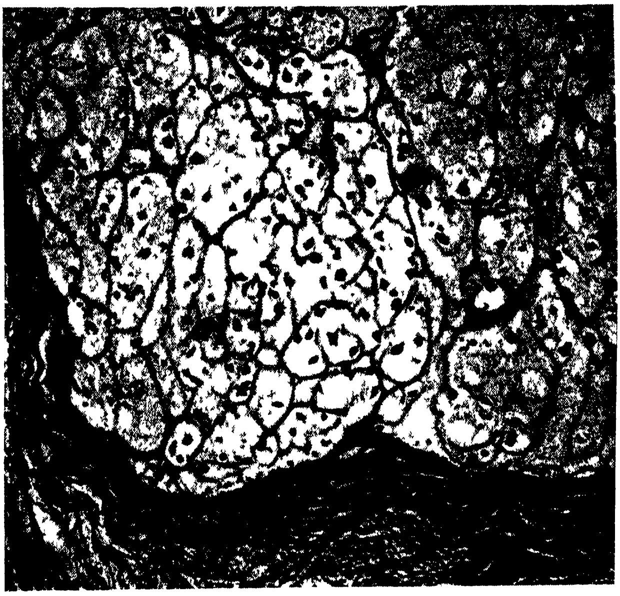


FIG. 138. *Chondroma,* showing irregular hyaline cartilage surrounded by comparatively non-cellular connective-tissue framework. Hæmatoxylin and eosin. × 90.

chondromas and certain other conective-tissue tumours are common, *e.g.*, chondro-lipomas and myxo-chondromas. Chondromas growing from the cartilages of the larynx, trachea and ribs (ecchondromas) are rare.

Cartilage may be found in teratoid tumours arising from certain glands, *e.g.*, testicle, ovary, mammary gland, parotid and the submaxillary. Ordinary chondromas show little or no tendency to become malignant, but, on the other hand, these mixed tumours may be, and not infrequently are, malignant and of the nature of chondro-adenomas or chondro-sarcomas, in which myxomatous degeneration is common. In the case of such tumours in the testicle and ovary, though some authorities regard them as due to the inclusion of portions of vertebral cartilages during development, a more probable explanation is that they are in reality "teratomatous" in nature (pp. 284, 292 and 351–2). In the case of the other organs mentioned, though a similar origin cannot be definitely excluded, portions of neighbouring cartilages—rib, ear or jaw—may have become detached during development and included as residues or "rests," subsequently giving rise to tumour-formation. Areas of cartilage are not infrequently found in teratomatous dermoid cysts.

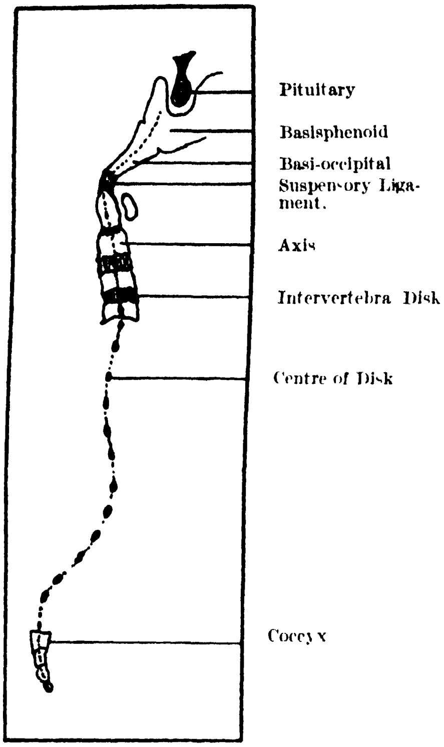


FIG. 139. Diagrammatic sketch illustrating situations where remnants of the notochord may occur in the adult. (After Sir Arthur Keith, "Human Embryology," 5th ed., 1933, Fig. 62.)

5. **CHORDOMA** (Figs. 140–1). Tumours bearing some histological resemblance to chondromas arise from the remains of the notochord (a structure of hypoblastic origin—*see* Fig. 192, p. 357), more particularly its extremities, tumours of sacro-coccygeal origin being slightly less uncommon than those arising in the spheno-occipital region below and behind the pituitary fossa (Fig. 139). Those originating from intermediate parts of the vertebral column are still more uncommon.

Chordomas are very rare tumours and their component cells exhibit a characteristic and progressive mucinoid degenerative vacuolation of their cytoplasm and less frequently of their nuclei. These tumours, though comparatively rarely malignant, are then usually so only "locally"—tending to infiltrate and destroy the neighbouring bony structures. Secondary growths occasionally occur at a late stage and when the primary tumour has attained a large size

6. **OSTEOMA** (*see also* p. 1226). Bony tumours may be composed of compact bone (**osteoma eburneum** or **ivory exostosis**), or of spongy bone (**osteoma spongiosum**). The former are usually small, and occur especially on the outer or inner table of the bones of the skull, but they may sometimes attain a considerable size, for example in connection with the orbit or frontal sinus. Bony tumours arising in the interior of a bone are called **enostoses**. These may occur in the interior of a long bone or in the bony sinuses of the skull, *e.g.*, in the frontal sinus (Fig. 792, p. 1226) or maxillary antrum. Spongy osteomas

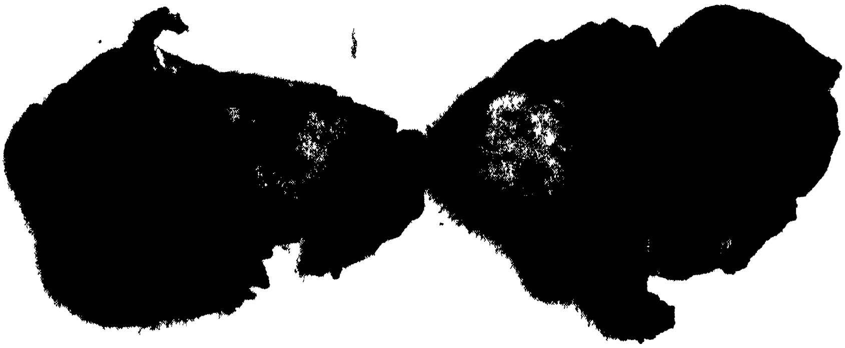
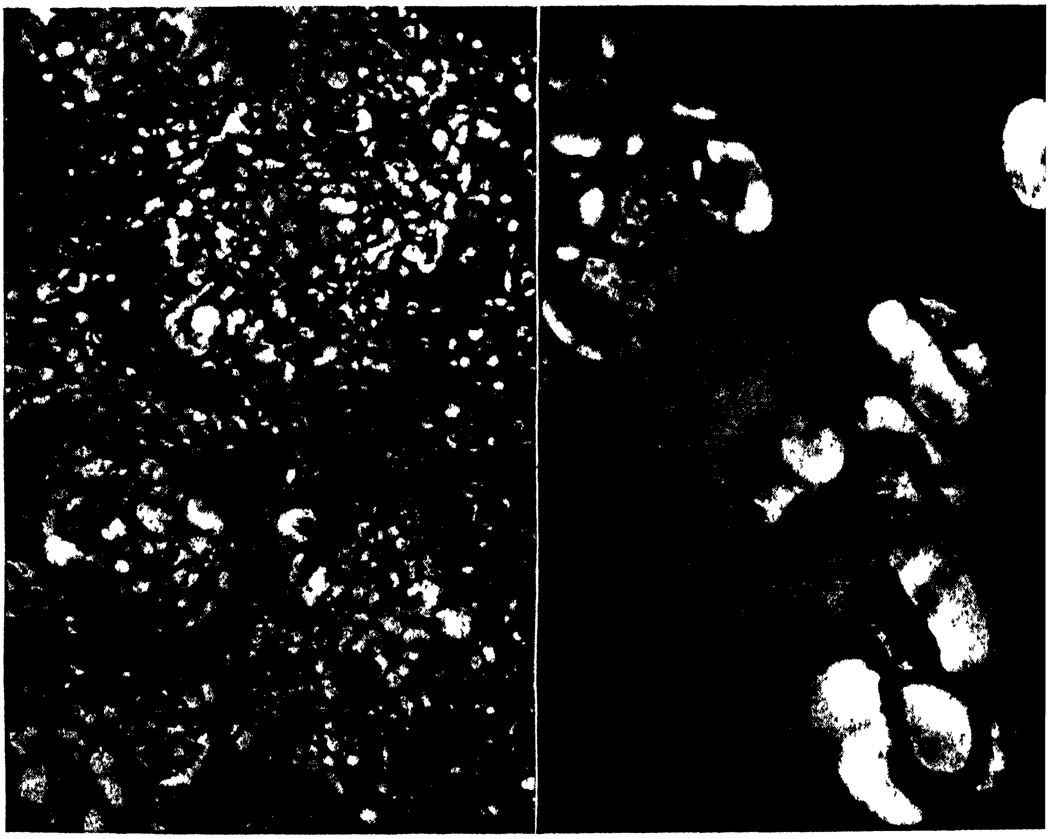


FIG. 140. *Spheno-occipital chordoma,* from which a fatal hæmorrhage occurred in a man aged 57, showing nodules of pale greyish-white cartilage-like tissue mixed with blood-clot. Natural size.



(A) × 100. (B) × 1,250.

FIG. 141. *Spheno-occipital chordoma.* Low-power and oil-immersion views of sections of the tumour illustrated in Fig. 140 above, showing the cartilage-like matrix and the characteristic vacuolated " physaliphorous cells" (so called by Virchow because of their containing mucin). (Carnegie Dickson, Worster-Drought and McMenemey's case. West End Hospital for Nervous Diseases, London.[1]) Hæmatoxylin and eosin.

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[1] *Jour. Path. and Bact.,* 1937, **44,** 41.

may attain a larger size ; and often, especially where they are multiple, originate as ossifying chondromas. Subungual exostosis of the terminal phalanx of the great toe is of this nature.

Outgrowths of bone or exostoses, when developing in connection with the attachment of muscles, are partly of the nature of hypertrophies and partly hyperplastic in character, and it is sometimes difficult to determine whether a given case should be classified along with these conditions or among true neoplasms. Such cases of multiple exostoses, especially where occurring in families, are now regarded as examples of " diaphysial aclasis "[1] (pp. 1226–27), rather than of tumour-growth.

Chronic inflammatory overgrowths, *e.g.*, the " osteophytes " of chronic rheumatoid arthritis and chronic osteo-myelitis, etc., should not be included as tumours. Occasionally, bony tumours—parosteal exostoses—are found among muscles in the neighbourhood of bones. These may arise from displaced osteogenic cells derived from the periosteum.

7. **ODONTOMA.** The term **odontoma** or **odontome** is applied to a considerable variety of tumours arising in connection with the teeth, either from the tooth-structures as a whole, or from one of the elements, *e.g.*, the dentine, enamel, etc. They may, in some cases, be due to abnormal development of the embryonal tooth-follicles.

(1) **Epithelial Odontomes** are usually cystic in character, and the following varieties are described :—

(i.) Multilocular cysts, fibrocystic disease of the jaw or adamantinoma. An ectopic intracranial variety of adamantinoma occurs occasionally in one variety of suprasellar cyst (pp. 350, 707, and 817–8).

(ii.) Eruption-cysts, due to proliferation of epithelium taking place in cases of delayed eruption.

(iii.) Dental cysts, commencing usually as a chronic infective " granuloma " and the formation of a so-called " epithelial root-tumour," in which a cyst lined by epithelium develops and may reach a considerable size, leading to expansion of the bone of the jaw.

(iv.) Dentigerous cysts or follicular odontomes probably in most cases produced by an infection originating in a deciduous tooth, and leading to the formation of a dental cyst which then surrounds and encloses the corresponding unerupted tooth.

(2) **Composite Odontomes** arise from the entire tooth-germ and many varieties have been described.

(3) **Connective-Tissue Odontomes** around a tooth may be fibrous and resemble a fibroma, and if these undergo calcification they are described as cementomes.

(4) **Malignant Odontomes** are rare tumours which arise as carcinomas or sarcomas from the tissues of the developing tooth-follicles.[2]

8. **OSTEOCLASTOMA or GIANT-CELLED TUMOUR OF BONE** (*see also* p. 1227 *et seq.*). In the past, two distinct conditions have been confused under the general term " myeloma " applied to them. These were the single, and by many pathologists regarded as comparatively " simple," giant-celled tumour arising in bone (formerly known as " myeloid sarcoma ") : and the multiple tumour-like condition arising in connection with bone-marrow and properly

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[1] From Greek κλάσις, *klasis*, in this connection having the significance of "modelling," hence "a-clasis" here means an absence or lack of modelling or shaping of the bone.

[2] For a fuller description of odontomes, books on General or Dental Surgery should be consulted.

described as " multiple myelomatosis " (p. 319). It is in certain cases of the latter only that Bence-Jones' proteinuria (p. 1231) may occur.

Here we are concerned only with the former of these two conditions, namely, the **osteoclastoma** or **giant-celled tumour of bone,** a variety of tumour which arises from the multinucleated or osteoclastic giant-cells and allied tissues of bone, *not* from any of the hæmopoietic marrow-cells proper, and the terms " myeloma " or " myeloid sarcoma " should, therefore, *not* be applied to it. Previously regarded as necessarily malignant, the tendency of more recent times to regard these giant-celled tumours as always simple in nature is equally unfortunate. Malignancy in a given tumour is *not* a phenomenon confined merely to the occurrence of metastases from it, but is also characterised by **local invasion and spread,** and of the latter process there are many and varying degrees of activity. The giant-celled tumours of bone are usually single, and, though they seldom give rise to **metastases,** such secondary growths are not unknown and may be found particularly after any form of interference with the original tumour. It is, however, essential to recognise that in varying degree these tumours are **locally invasive** and may become more actively so after incomplete surgical removal or radiological treatment, spreading especially along the marrow in the interior of the affected bone, for example, upwards within the shaft of the femur when the original site has been in the lower end of that bone. Such tumours are commonest in adolescents and young adults, and are found most frequently in the upper end of the tibia and the lower end of the femur : less frequently at the lower end of the radius and the upper end of the humerus.

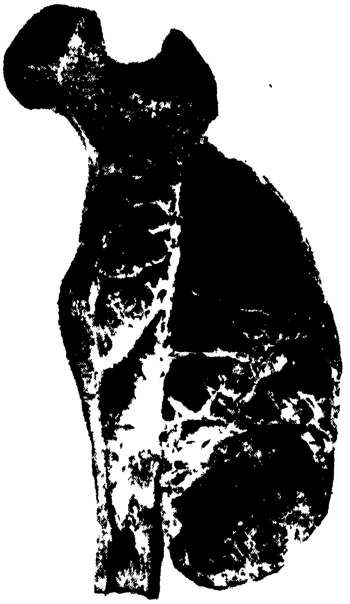

FIG. 142. *Giant-celled tumour of shaft of femur.* Macerated and dried specimen, showing expanded shell of bone.

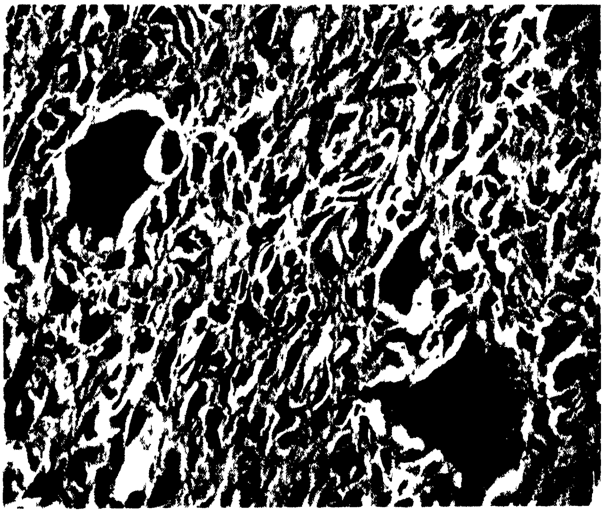

FIG. 143. *Giant-celled tumour of bone.* Multinucleated giant-cells amongst a background of irregular spindle-cells. Hæmatoxylin and eosin. × 300.

They may occur also at the proximal end of the clavicle and in the lower and upper jaws (the so-called " myeloid " epulis). Elsewhere they are rare. In the case of the jaw, the tumour appears to grow from the periosteum, whilst, as already mentioned, osteoclastomas as a whole develop usually from the cancellous tissue of the interior of the bones from which they grow, producing gradual absorption and expansion (Fig. 142). The expanded surface-layer of bone may become so thinned that " egg-shell crackling " may be felt on firm pressure over the tumour. On section, the tumour may be white, or pinkish-white, especially at the growing margins, the central part being usually mottled with dark red or brownish-red areas of hæmorrhage. These appearances are certainly highly *suggestive* of those of a malignant tumour. The amount of bone in these growths varies greatly in different specimens, from very open, spongy bone up to practically complete absorption, with perhaps only a few scattered spicules here and there.

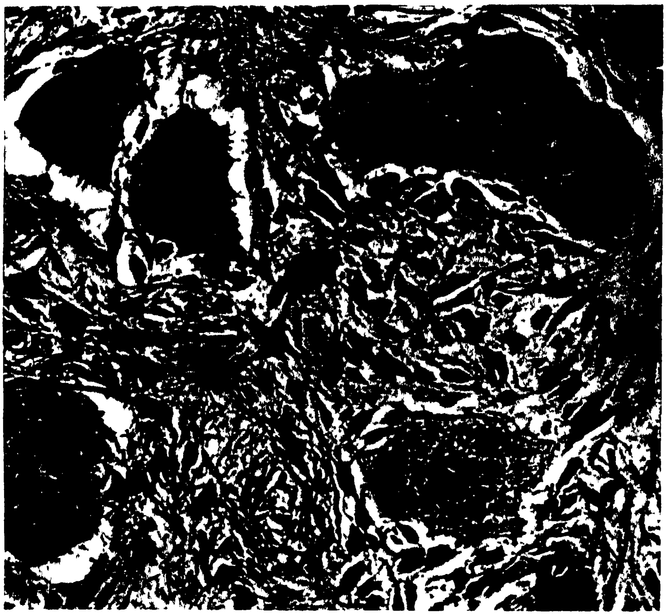

FIG. 144. *Giant-celled tumour from jaw.* The tumour consists of spindle-cells, amongst which are embedded numerous large multinucleated giant-cells. Hæmatoxylin and eosin. × 300.

Microscopically, the tumour consists of a groundwork of more or less undifferentiated, ovoid or spindle-shaped cells, very like those of a spindle-celled sarcoma, amongst which are scattered the giant-cells characteristic of the tumour. These giant-cells vary in number and size in different specimens and in different parts of the same tumour, and are derived probably from the osteoclasts of the fibrous reticulum of bone. The cells may attain a very large size and show an enormous number of nuclei (Figs. 143–4).

The tumours are always highly vascular, the vessels being delicate and very liable to rupture—hence the presence of the hæmorrhages which are one of the characteristics of the tumour. The condition of multiple myelomatosis is described on pp. 319, 320 and p. 1231.

9. **LYMPHOMA.** Owing to the fact that lymphadenoid tissue reacts with great readiness in many diseases, more especially in those of a septic and infective nature, and that this reaction often includes a process of hyperplasia, it is apparent that the increase in bulk of lymphoid tissue associated with many conditions tends to resemble tumour-formations arising in lymphoid tissue; and many disorders affecting it have, at some time or another, been classified as tumour-formations of lymphoid areas. In lymphadenoid goitre, there is an analogous transformation of the stroma of the thyroid into a tissue indistinguishable from ordinary lymphoid tissue (p. 831).

Quite apart, however, from hyperplasias and from lymphosarcomas (*see* p. 1264), true lymphomatous tumours do occur, for example in the mediastinum, in which they may arise from the thymus or from lymph-nodes : or in the abdomen, where they may form large masses. Histologically, they closely resemble normal lymphoid tissue, the reticulum and endothelium being well developed, and the lymphocytes being in their normal ratio to these constituents. In **lymphosarcomas,** on the other hand, there is an enormous increase in the lymphocytes and a corresponding deficiency in the endothelium and reticulum, these tumours being practically small round-celled sarcomas of very primitive type. For a note on **lympho-epithelioma,** *see* p. 339. In the chest, metastatic growths arising from oat-celled bronchial carcinomas (p. 571) and invading the mediastinum or heart have sometimes been mistaken for lymphomatous and lymphosarcomatous tumours. **Lymphatic leukæmia** is regarded by many, with whom we are inclined to agree, as a malignant neoplastic condition of lymphadenoid tissue, including that of the bone-marrow (p. 631 *et seq.*)

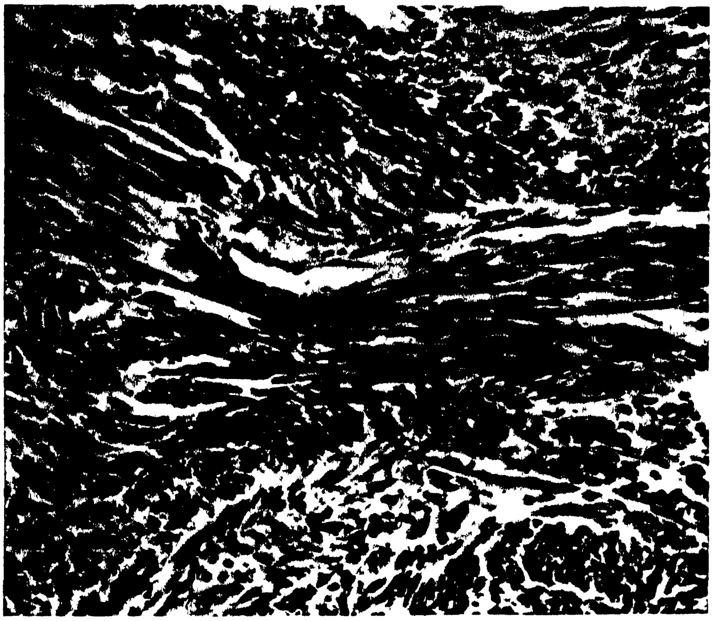

FIG. 145. *Leiomyoma uteri,* showing non-striped muscular fibres running in bundles cut in various directions. Hæmatoxylin and eosin. × 200.

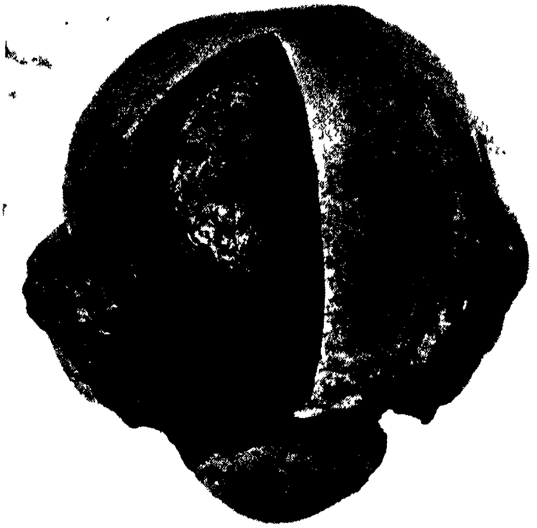

FIG. 146. *Large single leiomyoma* embedded in muscular wall of the fundus uteri. The vessels of the specimen have been injected, showing the comparatively poor blood-supply of the tumour as contrasted with the darker uterine muscle, into the numerous blood-vessels of which the injection has freely passed.

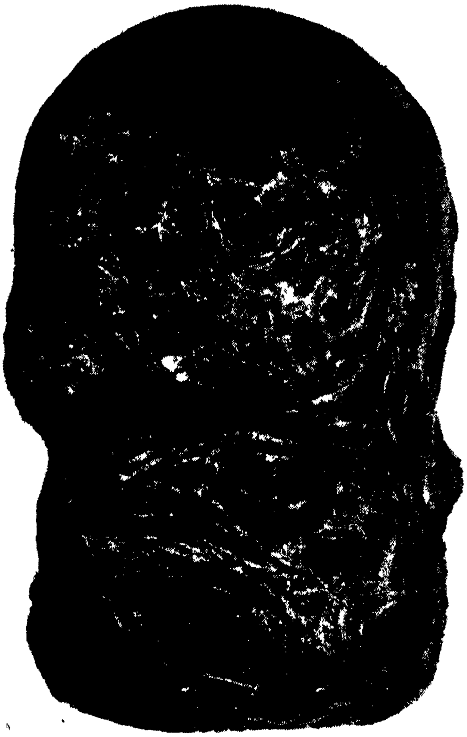

FIG. 147. *Multiple leiomyomata of uterus,* showing " watered-silk " appearance on section.

10. **MYOMA.** Tumours of muscle may originate either from smooth or from striped muscular tissue, and are termed leiomyomas and rhabdomyomas respectively.

Leiomyomas are very common, and their most frequent site is the uterus, (p. 922), where, though true muscle-tumours, they have unfortunately been named uterine " fibroids." They are composed of irregular bundles and whorls of non-striped muscular fibres, supported by a varying amount of fibrous-tissue stroma containing blood-vessels (from the muscular coat of which it is believed by some authorities that these tumours may be derived). The intermingling of the more translucent greyish-white muscle-fibres with the glistening white bundles of fibrous tissue gives to the cut surface of these tumours an appearance suggesting that of " watered silk " (Figs. 146 and 147, opposite). They are usually distinctly less vascular than the muscular wall of the uterus itself, and are therefore slightly paler in colour. They may have a pale pinkish tint, especially if their vessels are congested.

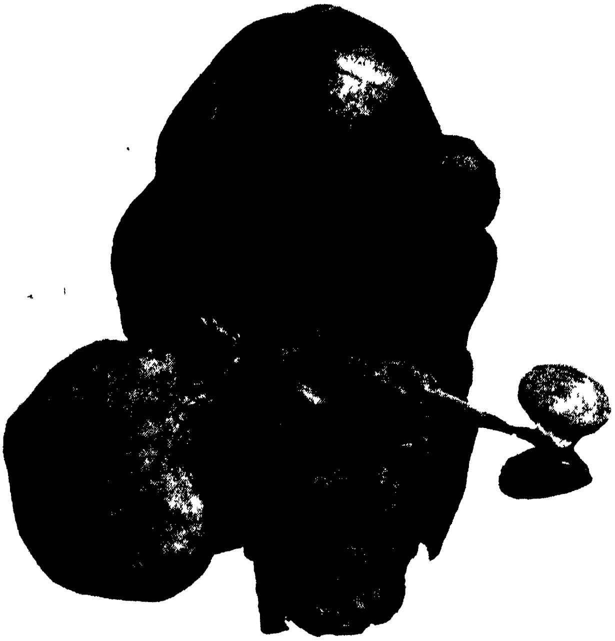

FIG. 148. *Multiple leiomyomata of uterus.* Some have become pedunculated.

Leiomyomas of the uterus are almost invariably multiple, and, in many such cases, the whole or greater part of the muscular wall of the organ may show a more or less diffuse change of a similar nature—the condition of **myomatosis uteri.**

Leiomyomas may occur also in the ovary, prostate, bladder, alimentary canal, including the œsophagus, and in the skin (in which they may be single [1] or multiple), originating, in the last-mentioned locality, it is said, from the erector pilæ muscles. They have also been described as growing from the muscular coat of subcutaneous blood-vessels, and they are recognised as forming, in some instances, pedunculated tumours in hollow organs such as the stomach.

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[1] " Solitary Cutaneous and Subcutaneous Leiomyoma," by A. Purdy Stout, New York, *Amer. Jour. Cancer*, 1937, **29**, 435.

Uterine myomas not infrequently attain a large size. They may be embedded in the muscular coat of the uterus, or they may project from the outer or inner surface, and they frequently become pedunculated (Figs. 146 to 148). If they contain much fibrous tissue, they are called fibro-myomas. The fibrous tissue sometimes undergoes a species of hyaline degeneration, with swelling and confluence of the fibrous bundles—the muscular tissue itself, however, not being affected by this process. Occasionally, sarcomatous transformation may supervene. Œdema, dilatation of lymphatic spaces (occasionally a marked feature), mucinoid and other degenerative changes, are common, and extensive softening may lead to the production of pseudocystic cavities. Localised, or in some cases extensive, necrosis occurs, usually from thrombosis of the vessels—the commonest cause of the "red degeneration" often associated with pregnancy. These tumours may become calcified, forming the so-called "womb-stones." A considerable degree of atrophy may occur in uterine myomas after the menopause.

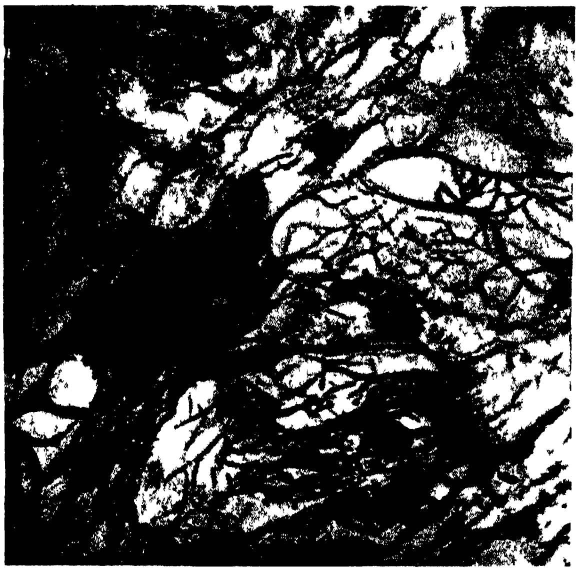

FIG. 149. *Rhabdomyoma*, with cells showing irregular bundles and networks of striated muscle-fibres. (From the same case as Fig. 720, p 1133.) × 450.

In **adenomyoma of the uterus,** proliferated gland-tissue of the mucous membrane, surrounded by a zone of cellular stroma, is mingled with the myomatous tissue in the wall of the uterus : and nodules of similar structure are found occasionally in the vaginal wall, broad ligament, ovary or in the peritoneum. When this phenomenon is more or less diffuse, *e.g.*, throughout the muscular wall of the uterus, the condition is known as **adenomyomatosis.** For a description of the analogous or allied conditions of endometrioma and endometriosis, *see* Diseases of the Female Reproductive Organs, pp. 922–3.

Rhabdomyomas, or tumours of striped muscular tissue, are extremely rare, and are usually "congenital." They may occur in the kidney or in the testicle, or some other part of the urogenital system, and, though possibly due, as some think, to the inclusion in these organs of some fibres of the lumbar muscles, they are probably teratoid or teratomatous in origin. Rhabdomyomas are sometimes found in the muscles of the lumbar or gluteal, or, though only very exceptionally, in other, regions. They may also occur in the myocardium (Fig. 149), and, in this position, as well as in the kidney and elsewhere, they may be part of the peculiar congenital "multiple-tumour syndrome" of tuberous sclerosis (*q.v.* p. 1134, and *cf.* pp. 291–2 and 473). The muscle-fibres of such tumours are usually imperfectly developed; the primitve cellular characteristics of developing tissue may be very pronounced, and the tumours can then hardly be differentiated from the sarcomas. The muscle-fibres may be mixed with cartilage, bone, or fat.

11. **GLIOMA (and GLIOBLASTOMA)**. The term "glioma" is a general one used in the past to describe any type of tumour arising from the interstitial glial tissue of the central nervous system. As is pointed out on page 1097 *et seq.*, where these tumours are described in detail, it is convenient to follow Bailey and Cushing in a consideration of all the various types of cell (some twenty in number) comprising the nervous system and to adopt a method of subdivision based on origin from, or reversion to, these various cells, if a workable classification of new growths of the nervous system is to be evolved (Fig. 679, p. 1098; and *cf.* Fig. 570, p. 952). It is sufficient here to point out that all these tumours, whilst varying considerably in malignancy, have the same general character of failing to produce metastases, except within the nervous system itself, and that only rarely (p. 1144)—perhaps because their cells are of so highly specialised a character that they fail to survive when transplanted among other tissues.

One variety of tumour usually described as a "glioma of the retina" and which occurs principally in children, contains no glial fibres or fibrils, and is described more accurately as a **retinoblastoma** (p. 1102). This tumour is at first of a locally invasive character, but later shows a more generally malignant behaviour and may, unlike the tumours arising in connection with the glial tissues proper, metastasise throughout the internal organs. **Medullo-epithelioma** of the retina, and the extremely rare "**mature**" or "**adult-celled glioma**"—the latter found in the retina practically only as part of the tuberous-sclerosis syndrome—are described on pp. 1110 and 1134.

12. **NEUROCYTOMA** (or "**Ganglioneuroma**"[1]) and **NEUROBLASTOMA.** These are rare tumours which occur only very occasionally in the brain or cord, but are slightly less uncommon in the peripheral nervous system, including the cranial (*e.g.*, the trigeminal), spinal and autonomic ganglia, and also in the suprarenal medulla (pp. 845–6). They are characterised by the presence of **neoplastic nerve-cells**[1] in varying number and in varying stages of development (hence our inclusion of the **neuroblastomas** along with them here). Tumours intermediate between the bi-potential medulloblastoma (p. 1099 *et seq.*) and the neuroblastomas and neurocytomas are, as noted by Percival Bailey, sometimes found in the neuraxis itself, *e.g.*, as the "**medulloblastoma neuromatosum**"

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[1] Note that the more or less obsolete term "*ganglio-neuroma*" here designates a tumour of "ganglionic" *nerve-cells in general,* and does *not* refer to the cells of nerve-ganglia in particular (*see also* pp. 845 and 1117). As the significance of the word is ambiguous and liable to misinterpretation, its use is best avoided. If special names are desired for the nerve-cell tumours arising *from nerve-ganglia,* they might conveniently be called "*gangliomas*"—those from the chromaffin system being termed "*paragangliomas.*"

(Fig. 686, p. 1103); and such tumours occasionally contain neoplastic nerve-cells in sufficient numbers to justify their classification as neuroblastomas or neurocytomas (p. 1114), *i.e.*, among the nerve-cell tumours proper (Figs. 700 to 704, pp. 1115 to 1117). For a note on the chromaphil (or "chromaffine") tumours or "phæochromocytomas" of the suprarenal medulla, *see* p. 846.

Tumours of peripheral nerves, particularly of the **nerve-sheaths (neurofibroma, neurolemmoma,** etc.) are discussed on pp. 1135–44: and also on pp. 298–301.

The bulbous or tumour-like nodules or swellings which develop on the lower ends of the upper or proximal portions of severed nerves in wounds and amputation-stumps, and which were formerly referred to as "amputation-neuromas," are *not* neoplastic in nature, but are merely cicatricial overgrowths of the connective-tissue sheath of the nerve, and may contain a varying number of aberrant nerve-fibrils which have proliferated in an attempt at bringing about regeneration (pp. 1141 and 1178–9).

(ii) MALIGNANT or ATYPICAL (MALIGNANT CONNECTIVE-TISSUE SERIES)

(a) SARCOMAS—MALIGNANT CONNECTIVE-TISSUE TUMOURS

The structure and other general characters of the sarcomas, which may be regarded as the atypical or malignant representatives of the group of tumours which has just been considered, have already, to some extent, been discussed. We may again emphasise the fact that we do not use the term "sarcoma" in an embryogenetic sense, *i.e.*, we do not restrict it to the malignant tumours arising from true mesoblast only, and we see no valid scientific objection to the inclusion in this group of any or all of the malignant or atypical pulp-tumours—whether epi-, meso-, or hypo-blastic in origin.

Sarcomas are pulp-tumours which remain or become cellular in type, with absence, or only slight and imperfect development, of definite tissue-characteristics. Most of them are mesoblastic in origin; but the malignant forms of **glioma** are epiblastic; and the very rare malignant **chordomas** arising from the remnants of the notochord are hypoblastic in origin. It should be remembered that, among the malignant tumours occurring in man, the sarcomas form a small group only, which are much less common than are the carcinomas or malignant tumours arising from epithelial structures. On re-examination, some old museum-specimens labelled "sarcomas" have been found to be highly anaplastic varieties of the latter group, for example bronchial carcinomas, which have also on occasion been mistaken for "endotheliomas" or "mesotheliomas." Similarly, certain specimens labelled "mixed-celled sarcoma" have proved to be anaplastic gliomata, *e.g.*, members of the glioblastoma multiforme group (p. 1103).

Whilst the sarcomas differ considerably from each other in histological and morphological characters, yet certain appearances tend to be common to all.

Owing to their rapid growth pushing aside the normal tissues, macroscopically they often *appear* to be encapsulated, but on microscopical examination the surrounding tissue is seen to be infiltrated by the tumour-cells. The tumours are usually hæmorrhagic and often show softened areas due to necrosis following upon hæmorrhage or thrombosis. Microscopically, the blood-vessels are seen to be very poorly-formed or even without any true formation or supporting structure at all, being represented by mere spaces among the tumour-cells. Definite stroma is usually absent, or at best poorly represented, which explains the lack of tissue-resemblance. Fine intercellular substance is present in varying degree, but may in some cases require special methods of staining for its demonstration. The cellular elements of the tumours vary with the type of growth, but consist always of actively proliferating cells of undifferentiated type; and mitosis, both typical and atypical, is usually a prominent feature of the cell-nuclei.

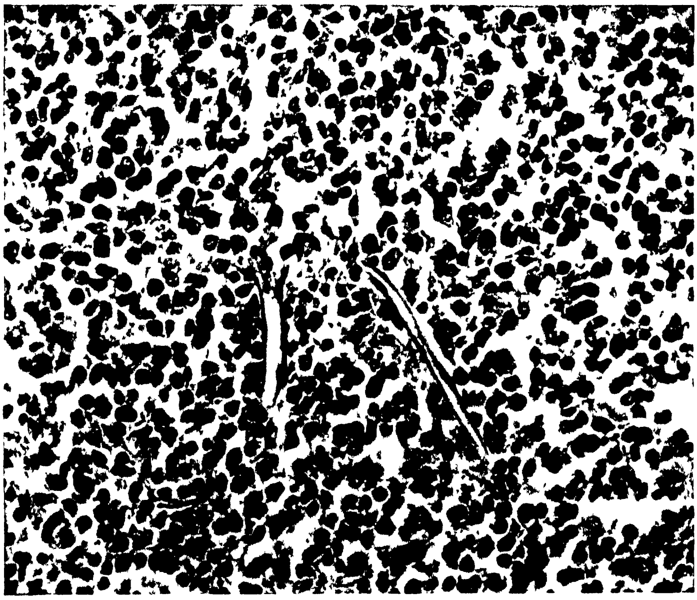

FIG. 150. *Small round-celled sarcoma* with thin-walled blood-vessels Hæmatoxylin and eosin. × 300.

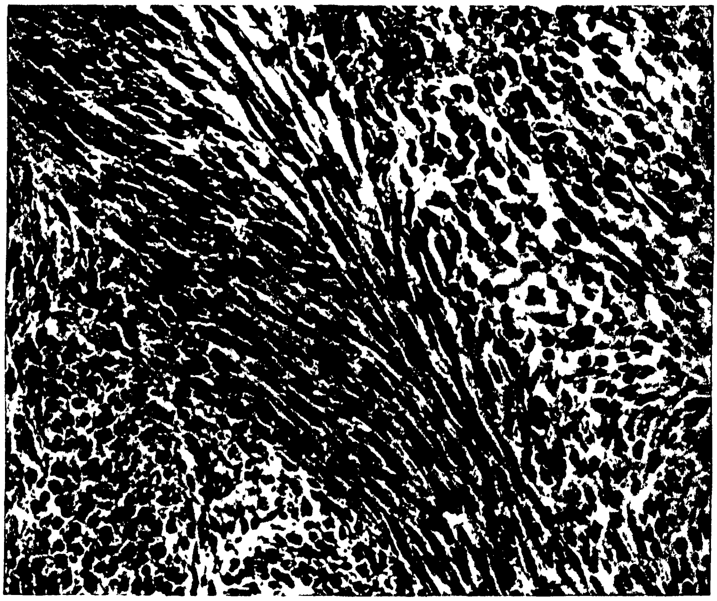

FIG. 151. *Small spindle-celled sarcoma*, showing bundles of cells cut longitudinally and transversely. Hæmatoxylin and eosin. × 300.

Classification of Sarcomas. Sarcomas may be classified according to—

i. **The variety, size, and arrangement of cells** present, *e.g.*, small or large round-celled or spindle-celled, mixed, etc.

ii. **The tissue towards which they tend to develop,** usually very imperfectly, *e.g.*, osteo-, chondro-, lympho-, fibro-, myo-sarcoma, etc.

iii. **The presence of pigment,** *e.g.*, melanoma. (Many melanomata, previously regarded as sarcomatous, are now classified as carcinomatous.)

iv. ***The presence of degenerative changes,*** *e.g.*, myxo-sarcoma, showing *"myxomatous" change.*

v. **Admixture with other types of tumour,** *e.g.*, with adenomatous, endotheliomatous, etc.

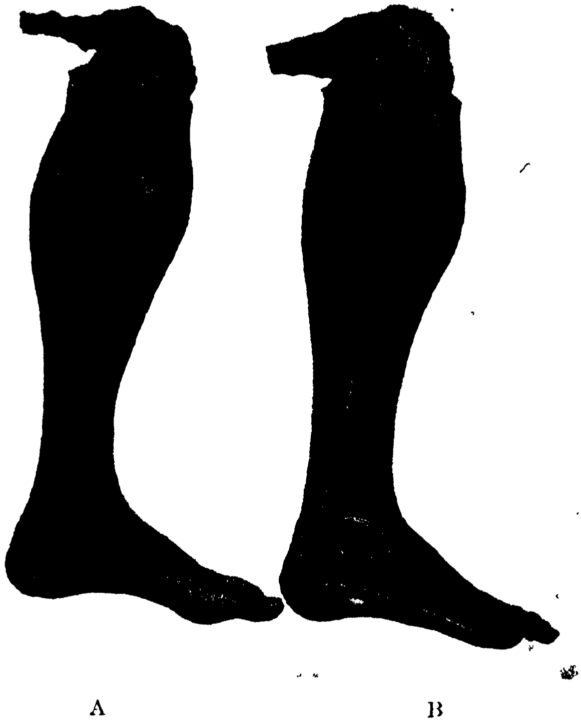

FIG. 152. *Malignant tumour of head of tibia,* probably a periosteal sarcoma. A, Surface view, showing tumour ulcerating through skin-surface. B, Antero-posterior section, showing large irregular malignant mass, originating from the head of the tibia, and infiltrating and replacing the tissues in the upper part of the leg.

(a) **ROUND-CELLED** and **SPINDLE-CELLED SARCOMAS** correspond roughly with the stages to be observed in the development of ordinary fibrous tissue. Thus—

(*a*) In **small round-celled sarcomas,** the cells are small and round, with scanty cytoplasm and darkly-staining nuclei. The intercellular substance is very scanty, granular, or only slightly fibrillated. The blood-vessels are numerous, very imperfectly formed, and badly supported. These tumours are among the most undifferentiated and most malignant known. A closely allied type of growth, the lymphosarcoma, will receive individual mention (p. 685).

(*b*) In **large round-celled sarcomas,** the cells have increased in size, but have not become elongated into spindle-shaped cells. The cytoplasm is more abundant, and the nucleus stains less deeply. The intercellular substance shows rather more fibrillation, the fibrils being more abundant and greater in thickness; and the vessels are less numerous, and distinctly better supported.

(*c*) In **small spindle-celled sarcomas,** the cells have become elongated and arranged in irregular bundles, but have otherwise remained in a comparatively primitive condition. There may be only very slight fibrillation, and the vessels are very imperfect.

(*d*) In **large spindle-celled sarcomas,** the cells are arranged in bundles, the fibrils are more numerous and thicker, and the vessels may be fairly well supported, *i.e.*, the tumour is not so rudimentary or anaplastic as the foregoing. It is often, however, not possible to tell the degree of malignancy of sarcomas from microscopical examination alone, and account must also be taken of their site and rate of growth. It is also sometimes a matter of great difficulty to differentiate certain sarcomas from granulation-tissue by microscopical examination alone.

(*e*) **Mixed-celled sarcomas** are tumours in which several of the above-mentioned varieties of cell-type may occur together (p. 1229). They sometimes also contain multinucleated giant-cells of various sizes; but in this connection it should be noted that examples of giant-celled glioblastoma multiforme tumours in the brain (p. 1103) have sometimes been so diagnosed in the past. The intercellular fibrillar material in mixed-celled sarcomas is scanty, and the vessels usually rudimentary.

Sites of Origin. These round- and spindle-celled and also mixed-celled sarcomas may arise from pulp-tissues in almost any situation, but especially from bone, fascia, and fibrous membranes.

Multiple Myelomas or Myelomatosis. In this condition, which is a neoplastic process in bone-marrow, numerous reddish or pinkish-white tumours are found in the marrow (Figs. 153–4), especially of the ribs, vertebræ and skull. These growths are composed of rounded cells, possibly derived from myelocytes or lymphocytes, though regarded by some as of the nature of plasma-cells, and it is possible that each of these varieties of cell occurs in different forms of the disorder (*see* p. 1231), and that certain very rare forms of marrow-tumour are derived from the erythroblastic series of cells (*see* pp. 1262–4). The condition usually produces profound anæmia.

In cases of myelomatosis, Bence-Jones described the occurrence in the urine of a protein substance (p. 279) which he believed to be of the nature of an albumose, though some recent writers consider it allied to, or identical with, the water-soluble globulin of the blood. A similar phenomenon has been described in certain cases of secondary carcinoma of the bone-marrow, leukæmia, and chloroma.

CHLOROMA (pp. 222, 636 and 1231). It is here convenient to mention a tumour of great rarity found very occasionally in children and still more rarely in adults, the blood showing a condition resembling that in leukæmia (pp. 625–36), the two conditions being now commonly regarded as closely allied, if not

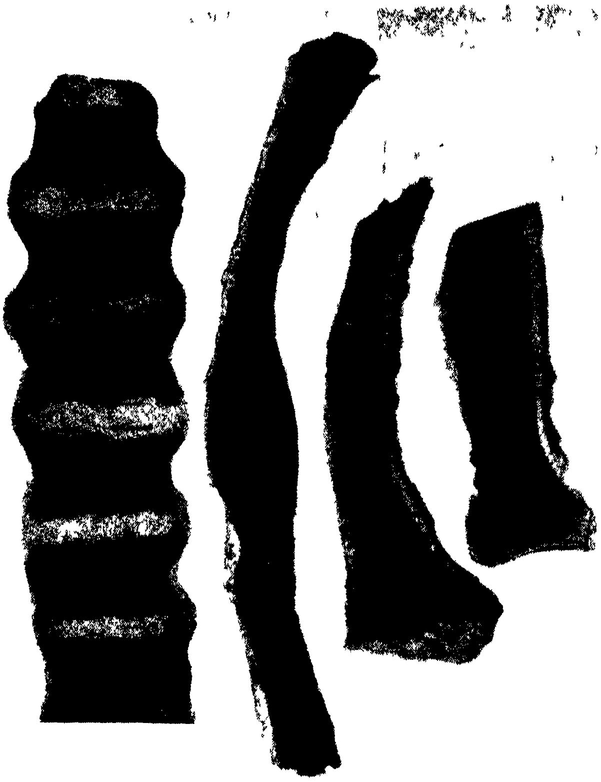

Fig. 153. *Multiple myelomas* in vertebrae, rib, clavicle and radius in a man aged 45 years. (By courtesy of Dr. Leila Hawksley, Royal Cancer Hospital, London.)

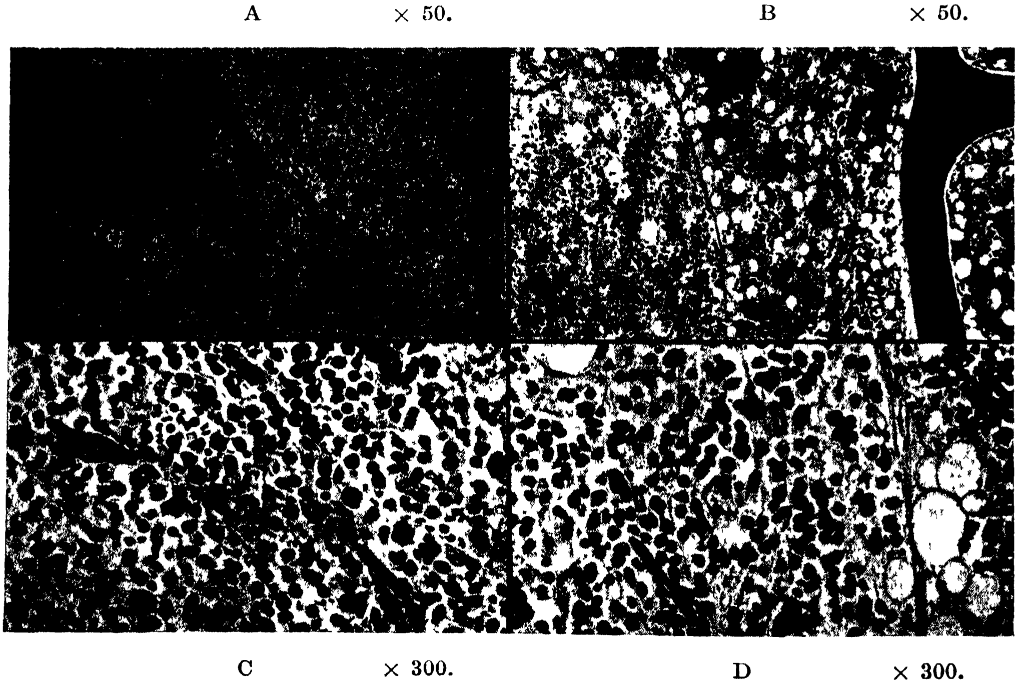

Fig. 154. *Multiple myeloma* in a man aged 60. (By courtesy of Dr. Leila Hawksley.)

A and B. Low-power views of the central and peripheral parts of one of the nodules. In (B) bone-marrow and a spicule of bone are shown to the right.

C and D are high-power views of the same, showing details, *e.g.*, the "lymphoid" character of the cells of the tumour. Hæmatoxylin and eosin.

practically identical. Chloroma occurs usually in the form of multiple greenish or greyish-green growths in connection with the bones, particularly the flat bones, and especially in relation to the periosteum. Areas of similar growth may occur also in the bone-marrow, kidney, liver, skin, and elsewhere. The colour rapidly fades on exposure to the air, but may be renewed by treating with a reducing substance such as a slightly alkaline solution of sodium hydrosulphite (1 per cent.), as suggested by Drs. Leila Hawksley and R. J. V. Pulvertaft. Microscopically, these tumours may be of lymphoid or of myeloid type.

(*b*) **MALIGNANT MESOTHELIOMA, ENDOTHELIOMA, and PERITHELIOMA.**[1] When reversion of these tumours to pulp-characteristics has occurred, they fall naturally to be described among the general group of the sarcomas. These tumours represent the malignant analogues (*see* table on p. 299) of the simple tumours described on p. 331. Such tumours, when malignant, tend histologically to resemble the carcinomas ; but in them a still further reversion may readily occur, and they may take on the characters of pulp-tumours. **Atypical mesotheliomas,** *i.e.*, malignant tumours of this group arising from serous membranes, *e.g.*, peritoneum, pleura, synovial membranes, tunica vaginalis, etc. : **endotheliomas,** arising from the endothelium of blood-vessels or lymphatics : and **peritheliomas**—a sub-variety of the latter arising from the endothelium of perivascular lymphatics—may show an " alveolar " or even an acinus-like arrangement, suggesting the structure of a glandular cancer ; whilst, in other specimens, and sometimes even in different parts of the same tumour, a typically sarcomatous arrangement of the cellular and intercellular elements may be seen. These variations have given rise to many cumbrous and quite unnecessary names, such as " cylindroma," " carcinoma sarcomatodes," " sarcoma carcinomatodes," " alveolar," and " plexiform " sarcoma, etc., under which terms members of this group have in the past been variously described. Malignant " endotheliomas " and " peritheliomas " as tumour-types are diagnosed much less frequently than formerly. There has been general acceptance of the view that many neoplasms which were thus designated are, in fact, **poorly-differentiated carcinomas.** This is particularly true of so-called " mesotheliomas " of the pleura, which are often more likely to have originated by spread from a bronchial carcinoma (p. 571). Similarly, the neoplasm previously called a "perithelioma," because of " cuffs " of cells around blood-vessels, may be either an ordinary sarcoma, or an encephaloid carcinoma or " soft cancer " which has acquired this appearance by the necrosis of the tumour-cells in all situations except immediately around the blood-vessels. The *reticulo-endothelial system* throughout the body is an important potential source of origin of certain of these tumours (*see* pp. 1262–4).

In this group may also be included the angiosarcomas or hæmangio-endotheliomas, now often described as **hæmangioblastomas,** as well as certain tumours arising from the meninges (hæmangioblastic meningiomas and meningotheliomas—pp. 332, 1084, 1096–7, and 1129–30).

The so-called **" psammomas "** or **" brain-sand tumours "** represent a psammomatous type of meningioma, growing from the membranes of the brain and cord and arising probably from arachnoid cells or villi. These are true

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[1] In this section reference is made also to certain of the benign or simple tumours corresponding to these.

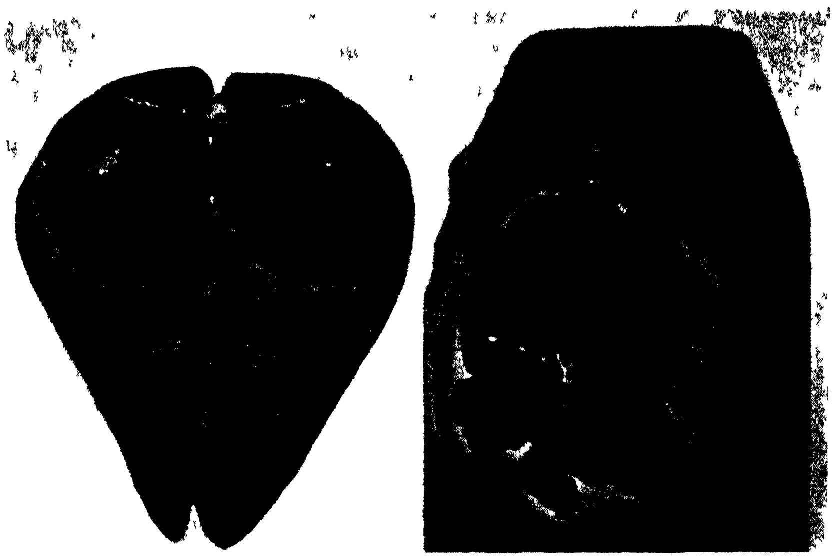

FIG. 155. *Malignant melanoma*, secondary nodules in spleen and liver. The site of the primary growth in this case was not identified.

tumours and vary from simple or benign up to locally-malignant and infiltrating growths (p. 1088 *et passim*). In structure, they usually exhibit concentric layers of somewhat flattened cells. The central cells of the whorls may become

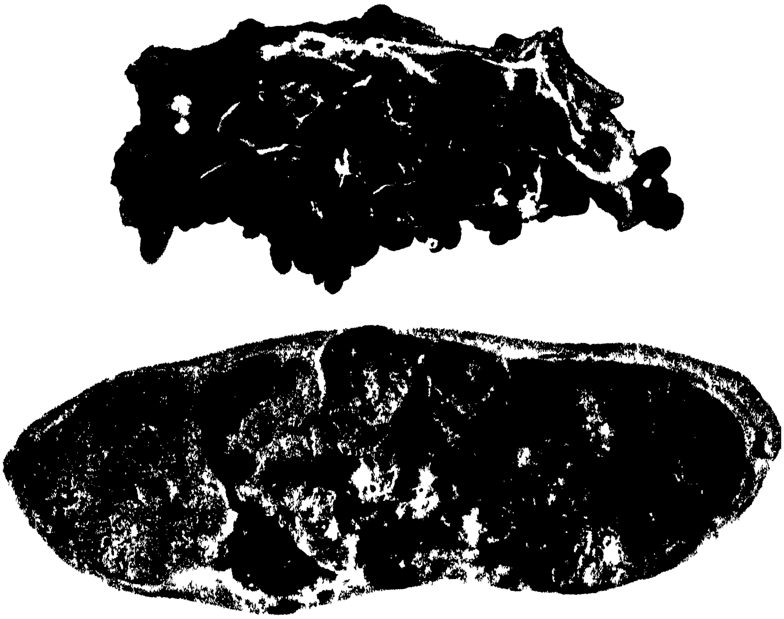

FIG. 156. *Malignant melanoma.*

Upper Specimen. Numerous secondary nodules of deeply pigmented tumour occurring in omentum.

Lower Specimen. Large secondary nodule in subcutaneous tissue. The melanotic pigment is irregularly distributed considerable areas of the tumour remaining unpigmented, but consisting largely of melanoblastic cells (see text).

calcified, following upon hyaline degeneration. A second type of " brain-sand nodule " is that found in the choroid plexuses and pineal body and represents a degenerative condition and *not* tumour-formation. These are known more correctly as **corpora arenacea** (pp. 213, 1122 *et seq.*).

(*c*) **Melanomas.** These are tumours in which some of the cells are pigmented and contain melanin (p. 219), an albuminous pigment which is elaborated by the tumour-cells. The presence of melanin, the amount of which varies greatly in different examples, gives to these tumours their typical sooty, brownish-black appearance. The distribution of this pigment in the melanomas may be patchy and irregular; and, in some instances, the cells of similar but unpigmented tumours may, by special staining- or impregnation-methods, be proved to contain the melanogens or uncoloured precursors of melanin : whilst by Bloch's " dopa " reaction [1] some cells containing pigment may be regarded as themselves capable of forming it, these being known as **melanoblasts** (or, when fully differentiated, as **melanocytes,** *i.e.*, containing melanin which they themselves have elaborated) as contrasted with mesoblastic phagocytic cells,

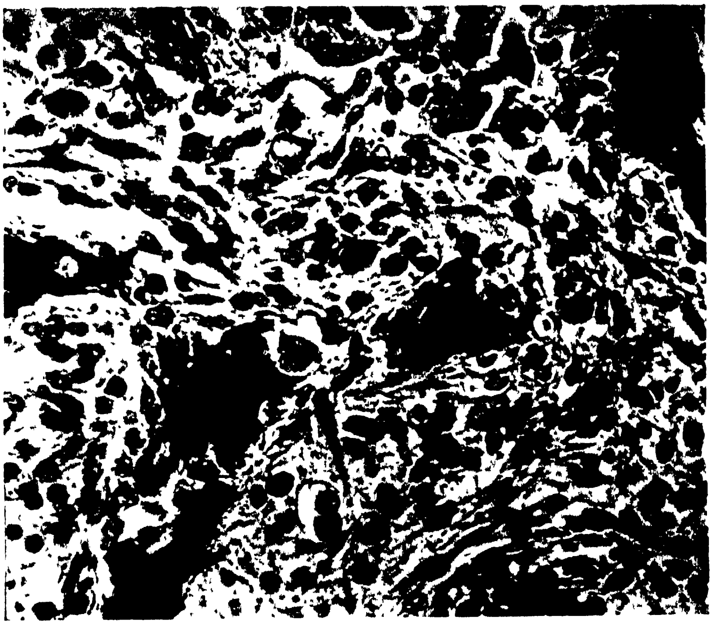

FIG. 157. *Osteo-sarcoma of head of tibia.* The dark areas are imperfectly-formed spicules of bone, embedded in a spindle-celled stroma. Hæmatoxylin. × 300.

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[1] Some aromatic substances such as tyrosine can, in the presence, within certain cells, of appropriate enzymes (oxydases), be oxidised to form coloured pigment. Bloch utilised the chemical substance known as Di-hydrOxy-PhenylAlanine (a name, as explained on p. 219, conveniently contracted to **DOPA,**) which, when oxidised in the presence of a suitable enzyme such as tyrosinase, has the property of becoming blackened, a change which occurs therefore when it is added to the cytoplasm of the specific cells containing the necessary enzymes, the reaction-product being " dopa-melanin." " Dopa-positive " cells, for example the pigment-containing epithelial cells in the deep layer of the epidermis, Bloch regards as (potential) melanin-*formers* or **melanoblasts** ; whereas the pigment-*containing* cells of the cutis vera he regards as mesodermal phagocytic cells which, according to his view, have merely ingested the pigment already formed by the epidermal melanoblasts. These mesoblastic phagocytic cells are dopa-negative and may be regarded merely as melanophores or melanin-*containing* cells only, and are therefore conveniently termed **melanophages.**

melanophages (by some called "**melanophores**" or pigment-carriers), which have merely ingested pigment already elaborated by other cells (*see also* p. 219).

Simple melanomas—melanocytomas—are represented by the pigmented moles and warts, common in the skin, congenital in origin, and of the nature of complex dysplasias or errors in the development of localised areas due to "mal-induction of perversely competent tissues" (p. 292). The pigment is contained in large or small spindle-shaped or irregularly rounded cells with long protoplasmic processes, often intermingled with undifferentiated "nævoid" cells seen in other forms of nævus (*cf.* p. 332). E. K. Dawson and her co-workers (1939),[1] following the conclusions reached by the late James W. Dawson (R. C. P. Laboratory, Edinburgh, 1925), as well as from their own extensive study of the cell-characters, distribution and method of spread of these tumours by lymphatics, believe that **melanoblastomas** in the human subject are essentially **epithelial** and **epiblastic** in origin, and should therefore be designated **melanocarcinomas.** Masson (1926) has suggested that these maldevelopments and the tumours derived from them arise from **cells of nerve-tissue type,** probably end-apparatus of the sensory nerves of the skin. In the **acanthotic type** of nævus, mainly the prickle-cells take part; whilst, in a third type, **various dermal elements** such as **neural** and **vascular tissues** also participate. The **melanoblastomas** and **melanomas** may arise from these pigmented moles [2] or warts in the skin, or from the uveal tract of the eye (choroid and iris), or, much more rarely, in the central nervous system (Fig. 677, p. 1095), especially from the pia over the medulla. These melanoblastomas are or may become extremely malignant, and metastases from them may occur in practically any and every tissue of the body. In the earlier stages, such secondary spread appears to be mainly by means of lymphatics, so that neighbouring lymph-nodes are first involved; but, later, spread is by the bloodstream also, and eventually a very widespread condition of metastasis results.

The characters of the cells of malignant melanomas vary considerably. Some are pigmented spindle-celled tumours, others are small round- or ovoid-celled tumours which are extremely malignant. In the case of the eye, the type of cell present determines the degree of malignancy of the growth, for, whilst the malignancy of the round-celled types is extreme, those tumours containing spindle-cells and many argyrophil fibres are of a less malignant type.

OSTEO-SARCOMA, CHONDRO-SARCOMA, and **MYXO-SARCOMA** have already been briefly described when dealing with the analogous simple tumours, and do not call for further remark.

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[1] "Debatable Tumours in Human and Animal Pathology. VIII. Melanoma," by E. K. Dawson, J. R. M. Innes and W. F. Harvey, *Edin. Med. Jour.*, 1939, **46**, 695; and "The Melanomata, their Morphology and Histogenesis," by J. W. Dawson, *ibid.*, 1925, **32**, 509.

[2] For the origin of the word "mole" *see* footnote on p. 924.

II. RIND-TUMOURS

(derived from "covering-" or "lining-tissues")

(i) SIMPLE OR TYPICAL RIND-TUMOURS

This group includes tumours arising from epithelial structures on the one hand (*e.g.*, adenomas and papillomas): and from endothelial structures on the other (*e.g.*, hæmangiomas and lymphangiomas).

(a) WITH ORIGIN FROM EPITHELIAL STRUCTURES:—

ADENOMAS OR TUMOURS ARISING FROM GLANDULAR STRUCTURES. In some respects it appears to be merely an accident of growth, whether the proliferating glandular tissue takes the form of a papilloma or *e*vagination, or gives rise to an adenoma or *in*vagination of the epithelium. In connection with all covering- and lining-membranes, whether epi-, meso-, or endo-thelial in nature, there are certain structural characters which should be borne in mind in considering the tumours which arise from them. Thus, in addition to the essential and specific covering- or lining-cells, such structures in normal circumstances also possess a basement-membrane and supporting connective-tissue stroma, as well as blood-vessels and lymphatics, derived from the mesoblast. In all true rind-tumours, the lining- or covering-cells appear to be the essential proliferating elements of the tumour, whilst proliferation of the supporting connective tissue and vessels is to be regarded as a result of this rather than as

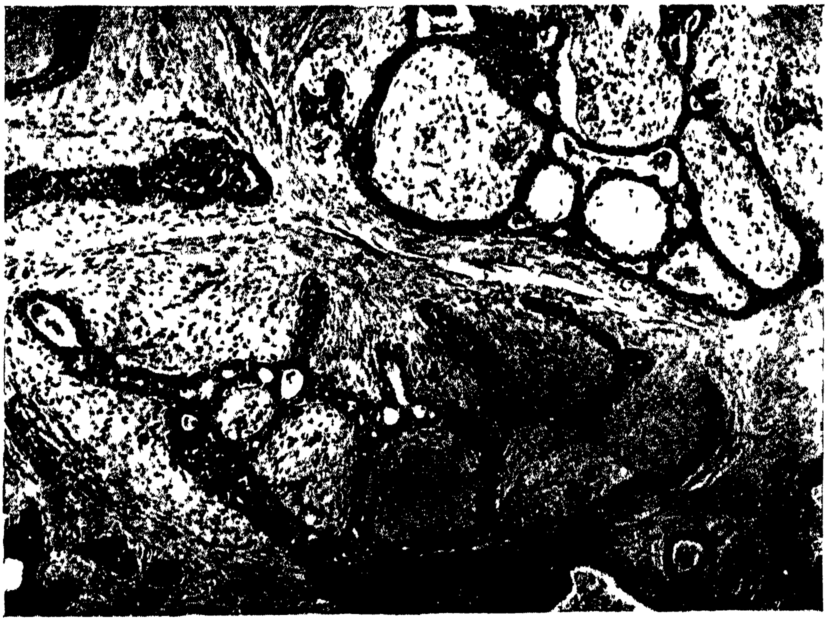

FIG. 158. "*Intracanalicular fibro-adenoma*" *of breast* (*see* footnote, p 944). It is often a matter of great difficulty to determine, in such tumours, whether the proliferation of the glandular, or of the connective, tissue should be regarded as the primary lesion. Hæmatoxylin and eosin. × 60.

an essential feature of the new growth. But it is difficult, in certain instances, to determine whether the primary overgrowth is not one of the subjacent or surrounding connective-tissue elements, with the epithelial proliferation increasing merely in order to preserve the continuity of the covering-layer of cells. To avoid this difficulty in nomenclature, such tumours, containing both proliferated epithelium and connective-tissue stroma, have been classed together by Ribbert and other writers under the common term fibro-epithelial tumours. Conditions such as chronic inflammatory overgrowths of fibrous tissue occurring in glands, accompanied by irritative overgrowth of the glandular epithelium (which occurs in some cases of "chronic mastitis" and "adenosis" (pp. 937 and 942–3), and which often simulate a fibro-adenoma in structure), have to be distinguished from true rind-tumour formation—not infrequently a difficult task in individual instances. Similarly, cystic dilatations, due to the mere blocking of tubules or ducts by inflammatory products, or by compression from without, must also not be confused with true adenomatous tumours. Chronic hyperplasias, often simulating and difficult to distinguish from neoplasias, may be due also to certain abnormalities, of the nature of deficiency, increase, or perversion of the secretion of some of the ductless glands, especially the pituitary and gonads, and these may come to react upon and cause changes in the structure of especially the prostate, breast and uterine mucosa.

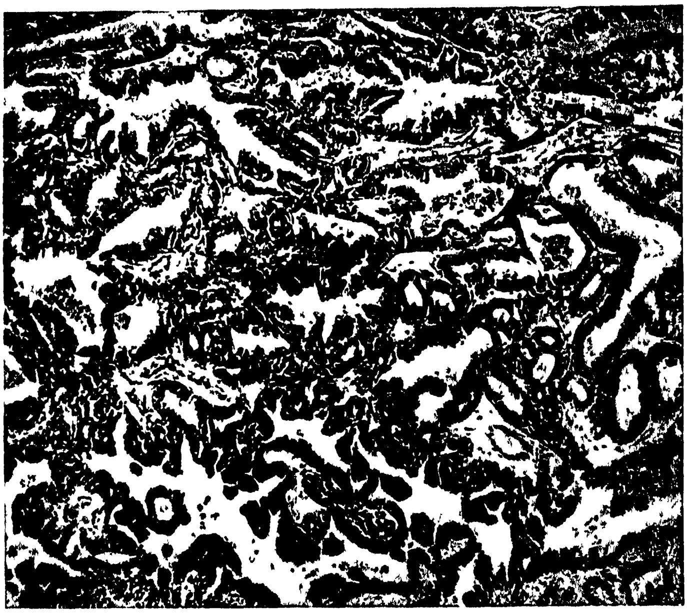

FIG. 159. *Complex adenoma of breast.* The acini are dilated and show numerous papilliform ingrowths or infoldings. Hæmatoxylin and eosin. × 50.

Histology of Adenomas (including Cysts)

Epithelium. The proliferation of the glandular cells, in the case of a tumour, often leads to greater complexity of structure than is found in the original gland. Thus, the cells may be increased to several layers in depth instead of an original single layer; sometimes papilliform ingrowths or infoldings occur, especially in cysts lined by rapidly-growing glandular cells. Alterations in the type of cell are common—for example, flattened or low cubical may replace columnar cells, or *vice versâ*. Individual cells often show great variations, they may be larger than those of the normal gland, or show abnormal variations in staining-reactions, and especially in the character, size and chromatin-content of their nuclei or other alterations in their minute structure, for example, ciliated cells may lose their cilia. Degenerative changes are common.

In tubular glands, the new formation of acini occurs usually as a process of budding from the pre-existing glandular tubes. In some instances, duct-like structures from which the tubules form, are the first to appear, and then enlarge, whilst in others the lumen may be imperfect or entirely absent. In the liver, anterior lobe of the pituitary, suprarenal cortex and elsewhere, the gland-cells themselves are arranged in solid columns or masses, and tumours arising from them usually show an analogous arrangement. In other instances —for example, in thyroid, cystic ovarian, parovarian and other tumours—the proliferating cells may be arranged in closed compartments, which become dilated and form **cyst-like spaces**; and, in some cases, multiple cysts are produced, *e.g.*, by exogenous budding, or by a further process of endogenous formation within the first cyst as it enlarges.

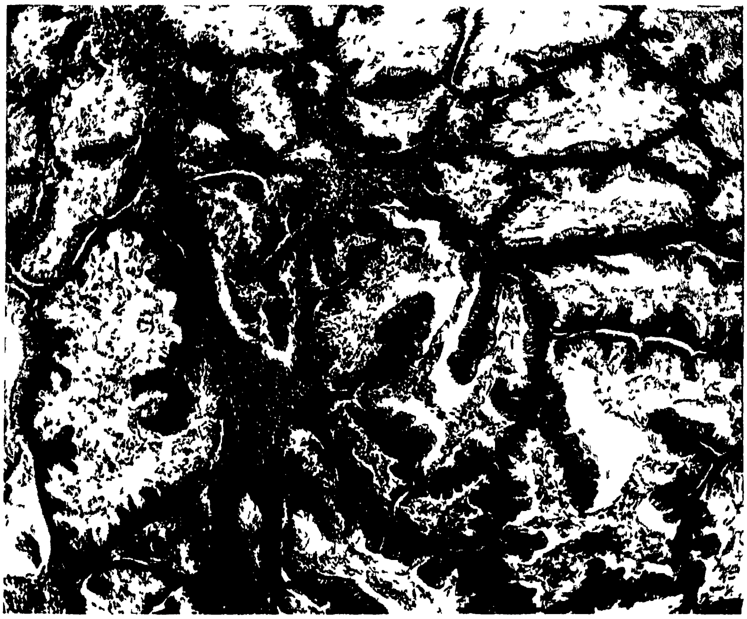

FIG. 160. *Compound cystic ovarian adenoma.* Cystic spaces lined by a single layer of columnar epithelium, showing numerous papillomatous ingrowths. Fibrous-tissue stroma. Hæmatoxylin and eosin. × 50.

Contents of Cystic Tumours. These tumours consist of hollow closed spaces containing fluid or semi-fluid contents of the nature of a secretion. This secretion is generally not of the normal type produced by the cells, but appears to form a necessary accompaniment of the growth of a cystic tumour. It may consist of a fluid containing certain mucin-like compounds of proteins and carbohydrates (p. 203 *et seq.*); or it may become thick and inspissated, and undergo various physical and chemical changes, such as the formation of cholesterol, fatty crystals, etc. In other instances, the secretion consists of altered and desquamated cells or their products—colloid, mucinoid and fatty material—and in some cases calcification occurs.

Supporting Structures. The stroma of adenomas varies greatly in character. In some tumours, *e.g.*, in the fibro-adenomas, it is firm and fibrous; whilst in others it is soft and cellular, perhaps "myxomatous," in character. There is usually, but not invariably, a basement-membrane in simple adenomas; and these tumours are generally enclosed in a fibrous-tissue capsule, developed by a condensation of the connective tissue of the organ in which they are growing. The blood-vessels of the stroma are, as a general rule, well formed and well supported. A lymphoid stroma is an essential element of the "adenolymphoma" of the salivary glands (p. 712), and we have observed a similar development of it around adenomas and adeno-carcinomas growing from the mucous glands of the laryngeal sinus.

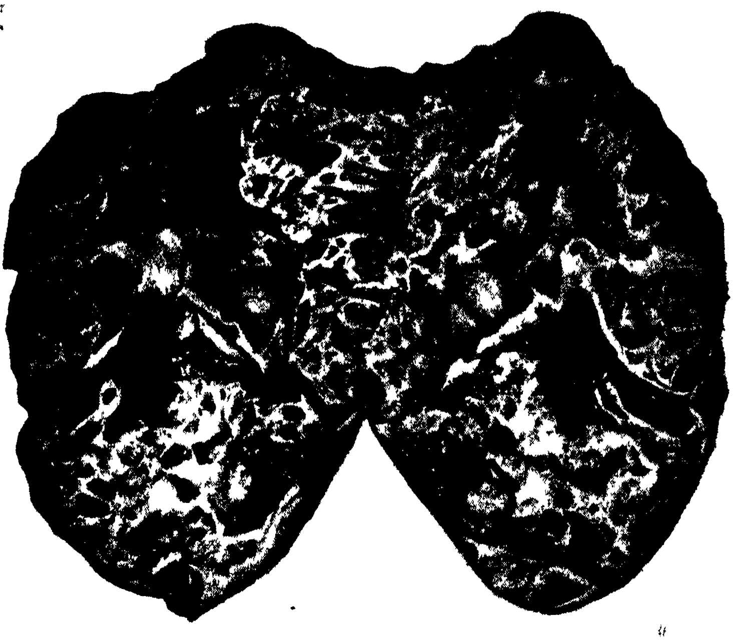

FIG. 161. *Compound cystic ovarian adenoma.* Large tumour containing numerous cystic spaces of various sizes.

PAPILLOMAS. Instead of being arranged in tubules as in adenomas, or forming closed spaces as in cysts, these tumours are outgrowths or projections, consisting of a central core of connective tissue containing blood-vessels, lymphatics, etc., and are covered by epithelial or some other form of "rind-cells." In some instances, there may be merely a single polypoid outgrowth;

in others, such an outgrowth may show branching ; or, again, as in multiple or " cauliflower " papillomas, there may be innumerable finger-like or villous processes closely massed together. As in the case of some members of the preceding group, it is sometimes difficult to determine which of these elements—connective-tissue cells or rind-cells—are the essential components of the neoplasm ; but probably, in the majority of instances at all events, the latter are to be regarded as such.

Varieties and Sites :—

i. **Squamous Papillomas.** These may grow from the surface of the skin, mouth, larynx, pharynx, œsophagus, anus, glans penis, cervix uteri, or vagina, *i.e.*, the parts of the body covered or lined by squamous epithelium. The normal relationship with regard to the relative position of epithelium to connective-tissue core, and of the various layers of the epithelium to one another, is maintained. The epithelial layers covering a squamous papilloma are frequently much thickened, especially in the harder varieties of this tumour, but otherwise there may be only slight divergence in the appearance of the cells (*e.g.*, prickle-cells, etc.) from those of the normal cuticle. The connective-tissue core may be cellular in some examples, more fibrous in others ; and it is usually highly vascular, the blood vessels being frequently thin-walled and somewhat

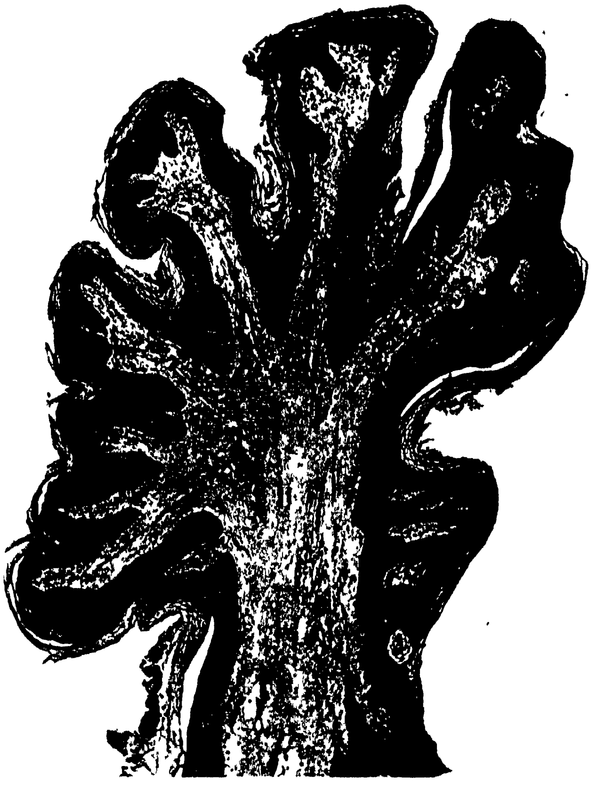

FIG. 162. *Squamous papilloma,* showing thickened skin-epithelium, covering a branching vascular connective-tissue core. Hæmatoxylin and eosin. × 38.

dilated. Secondary inflammatory changes, *e.g.*, leucocyte-infiltration, are common. In certain specimens, the connective tissue may closely resemble sarcomatous tissue.

Some skin-papillomas are congenital, whilst others may result from chronic irritation, *e.g.*, in petroleum-workers. The " condylomata " and the " cauliflower-papillomas " sometimes developed about the genital organs in syphilis and gonorrhœa closely simulate squamous papillomas, from which, histologically at all events, they cannot be distinguished. They may result from the irritation caused by the discharges, or may be definitely infective in nature. The common cutaneous wart—though structurally identical with a papilloma—and the condition known as molluscum contagiosum, are due to filtrable viruses (p. 123) and can be reproduced in man by the intradermal introduction of the filtrate of emulsions of the infected tissue. At present, these lesions are not considered truly neoplastic.

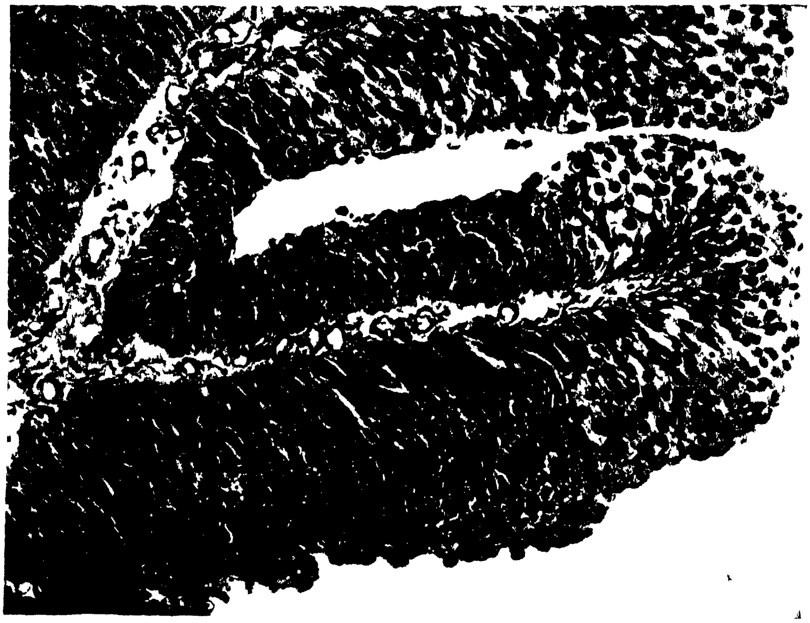

FIG. 163. *Mucosal papilloma of bladder*, composed of long slender branching processes with delicate vascular cores covered by proliferated transitional epithelium—the so-called villous papilloma. Van Gieson and hæmatoxylin. × 200.

ii. **Mucous** or **Mucosal Papillomas** may grow from any mucous membrane, but are found especially in the larynx and trachea, alimentary canal, bladder, pelvis of the kidney, uterus, and in various glandular ducts. Polypoidal growths in the nose, naso-pharynx and larynx are also common, but these in the majority of instances are now regarded by most authorities as chronic inflammatory overgrowths, which become polypoidal owing to the traction of the air passing backwards and forwards over their surface. Similarly, the polypoidal growths which are of frequent occurrence in the large intestine, especially above a stricture, may be due to irritation and the traction of the intestinal contents. Polypi so originating, however, not infrequently become the site of true neoplastic transformation. **Multiple polyposis** of the intestine is found in certain families and these papillomas tend to become malignant. In the bladder, papillomatous tumours, or villous papillomas (Fig. 163), may be composed of long, delicate, branching processes, the softer varieties of which, especially if examined floating in a fluid medium, are not unlike certain seaweeds in naked-eye appearance, whilst the former varieties have a more compact "cauliflower" arrangement. Fragments readily break off and are passed in the urine, and may be associated with intermittent hæmaturia. These tumours are very apt to be malignant and locally invasive. An analogous growth is found occasionally in the uterus—the so-called villous tumour of the endometrium (Bland Sutton) or **papilliferous adenoma.** It occurs in elderly multiparæ, and tends to invade the wall of the uterus locally, but does not give rise to secondary growths elsewhere.

iii. **Papillomatous Ingrowths from the Walls of Cystic Tumours.** These are mentioned in the section dealing with cysts (p. 327). As in adenomas, the cells of papillomas show considerable variations and aberrations, with alteration in type and arrangement.

(b) WITH ORIGIN FROM ENDOTHELIAL STRUCTURES

(arising from Vascular and Serous Endothelium)

Tumours arising from blood-vascular or lymph-vascular endothelium, from serous membranes, and certain other endothelial structures, are classified, according to Adami, as transitional rind-tumours or lepidomata, *i.e.*, they are derived from rind-tissues which are themselves in turn derived from pulp-tissues. Such tumours may, therefore, retain their lining-membrane character, as in the simple tumours derived from vascular endothelium; but, on the other hand, they may revert to the more primitive characters of pulp-tumours, and so come to resemble sarcomas.

ANGIOMA. Tumours composed of vascular tissue may arise from blood-vessels (**hæmangiomas**), or from lymphatics (**lymphangiomas**), the endothelial lining of these being apparently the essential constituent of such tumours—although, as explained on page 325, supporting-tissues usually accompany the lining-endothelium; and proliferation of the muscular coat of arteries or veins may also occur in some instances. The endothelial cells may remain in a single layer, or they may proliferate to form two or more layers, and occasionally there may be a distinct perithelial type of growth. In certain rare instances, the cells may proliferate to form papillomatous ingrowths, projecting into the cavities, a process analogous to that occurring within some adenomas and cysts. Thrombosis, and the processes which follow it (pp. 161–7), may take place in the blood- or lymph-contents of the vascular spaces. Both varieties of angioma are usually "congenital" in origin and are regarded by some as being of the nature of a persistence of an embryonic meshwork of vessels rather than neoplastic. The production of metastases from primary endotheliomatous growths (**angioblastomas**) has, however, been described, and in certain instances it is difficult to avoid the conclusion that the tumour represents a malignant form of endothelioma.

1. **Hæmangioblastomas, hæmangiomas** or **angiomas,** may be composed of proliferated and dilated vessels—arteries, veins, or capillaries, as the case may be—and are then known as **plexiform angiomas**; or they may consist of irregular intercommunicating blood-containing spaces, the **cavernous angiomas.** All gradations between these two forms occur. The commonest variety of plexiform angioma, the so-called **congenital vascular nævus**[1] or "birth-mark," is formed of dilated, thin-walled capillaries or veins. Its commonest situation is the skin.

One characteristic variety of angioma occurs as a projecting, rounded, red or bluish-red, pulsatile mass, usually situated on the scalp, and from which hæmorrhage from ulceration or injury is liable to occur. It is congenital in origin; and, histologically, such a tumour may be composed of dilated endothelial capillary spaces, or of very imperfectly formed vessels resembling thin-walled veins. Hæmangiomas of the central nervous system are described on p. 1129. They may form one element in some of the multiple-tumour syndromes (p. 1130 *et seq.*).

Arterial angiomas are less common, and are found as congenital tumours *e.g.*, on the scalp.

Cavernous angiomas are commoner than the foregoing varieties. They are found in the skin or subcutaneous tissues, in the central nervous system, and sometimes in, or on the surface of, the internal organs, especially immediately under the capsule of the liver (p. 781 : and Figs. 164–5 opposite), or occasionally in the substance of the kidney. By some authors these are regarded as fibromas containing dilated intercommunicating vascular channels; whilst others are inclined to deny that they are of the nature of true tumours, considering, them rather as dilatations of normal blood-spaces, or channels occurring in areas in which the ordinary cells of the part have failed to develop, the term "hamartoma" having been coined to designate such a supposed "failure-tumour." It is at times difficult to determine whether certain individual examples of cavernous angioma do or do not possess an endothelial lining, or whether the spaces are lined directly by connective tissue. Some writers describe cavernous angiomas as a variety of venous hæmangioma, the partitions between the spaces being regarded as being derived from, or having the same structure as, the valves in veins.

Certain mixed vascular tumours, *e.g.*, those originating from the pituitary and pineal bodies or from the suprarenal, parotid, etc., are due probably to embryonic intermingling. The hæmangio-epitheliomas, hæmangioblastomas or "hæmangiosarcomas" sometimes observed in the liver (p. 783), parotid, bone, or, more rarely, in the subcutaneous tissues, have probably a similar origin.

2. **Lymphangiomas.** As in the case of blood-vessels, mere dilatation and varicosity must be differentiated from true tumour-growth. Thus, the lymphangiectatic swellings due to the presence of *Wuchereria* (*Filaria*) *bancrofti*, and the retention-cysts so frequently seen in the lacteals of the intestine and mesentery, should not be included here. It is very doubtful whether the diffuse congenital enlargement of the lymphatics of the tongue (macroglossia) or of the

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[1] The term "nævus" is applied to two differing conditions, the vascular nævus or angioma, and the nævus or mole, often pigmented, and usually not highly vascular. Occasionally the two conditions co-exist, but there is generally a clear distinction between the two. Mixed-cell nævi may contain varying admixtures of hairs and hair-follicles, sweat- and sebaceous glands, and undifferentiated "nævoid cells."

lip (macrocheilia) should be included as tumours. True lymphangiomas are probably always " congenital," and are usually of the cavernous variety. They may be found in the skin and subcutaneous tissue (*see* Fig. 165A, in Appendix, p. 1254), especially of the neck and face (*e.g.*, as the so-called **cystic hygroma**), or,

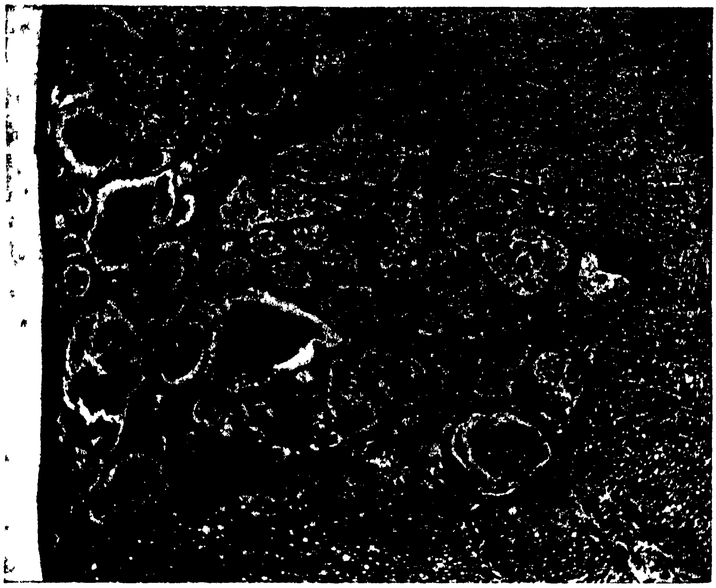

FIG. 164. " *Cavernous Hæmangioma*" *on surface of liver*, showing vascular spaces surrounded by connective-tissue stroma. Hæmatoxylin and eosin. × 28.

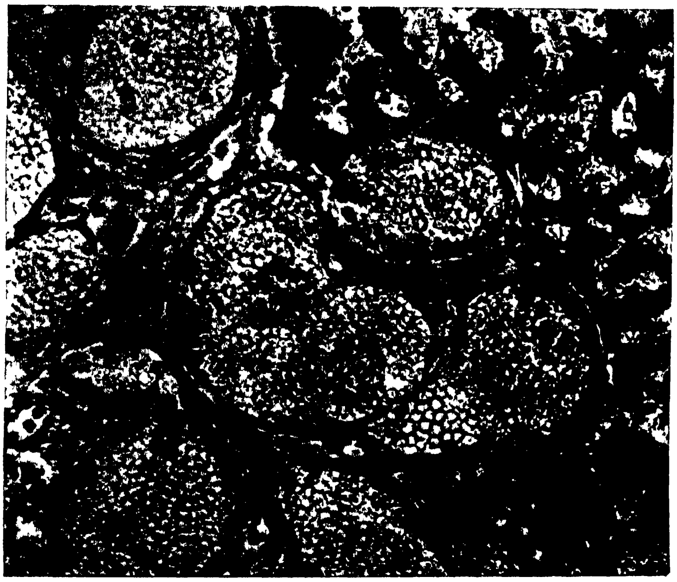

FIG. 165. " *Cavernous Hæmangioma* " *of liver*, showing thin-walled vascular spaces lined apparently with endothelium, and filled with blood. Liver-tissue is seen at right-hand part of section. Hæmatoxylin and eosin. × 250.

more rarely, in the ovary or in the hilum of the kidney. Except for the fact that they contain lymph in place of blood, these tumours closely resemble the analogous blood-vascular tumours.

(ii) MALIGNANT OR ATYPICAL RIND-TUMOURS

(The Cancers or Carcinomas, Malignant Tumours of Epithelial Tissues)

The essential element of tumours of this group appears to be the proliferating epithelial cells, which " invade " or " infiltrate " the subjacent or surrounding tissues. The stroma or supporting connective-tissue framework and the vessels of the tumour, are either those of the part invaded, or are formed by proliferation of these. The epithelium may show some, and frequently very pronounced, deviation from the original type in character or in arrangement. Thus, in scirrhous cancers, the original glandular arrangement is largely lost, and the cells form solid groups or masses lying in spaces surrounded by dense proliferated connective tissue. Further, aberrations in the size, as well as in the type, of the cells are common, as are also various degenerative changes of a colloid, mucinoid, or fatty nature. Mucinoid (" myxomatous ") degeneration may occur in the stroma. On the other hand, the proliferated epithelial cells frequently retain—though often very imperfectly—certain of their original characteristics : for example, the arrangement in acini in the case of malignant adenomas or the presence of " prickle-cells " in acanthomas [1] or squamous epitheliomas.

Method of Growth. As in the case of the preceding group, cancers may form excrescences and papillomatous outgrowths on a surface, or rounded or irregular nodules in the substance of the tissues. These points have been sufficiently described in the chapter upon the general characteristics of tumours ; and it need only be added that cancers may **spread locally,** mainly by infiltrating lymph-spaces and lymphatics ; or may **form metastases** in distant parts, this dissemination occurring chiefly by way of the lymphatics, but also, in some instances, by the blood-stream. In the case of spread by the lymphatics, two conditions may occur : either an infiltration or " permeation " along lymphatic vessels, or a process of embolism by which carriage of cells in the lymph-stream takes place. These two methods are often combined in varying degree in any given case.

VARIETIES OF CARCINOMA

(*a*) Squamous-celled Carcinomas or Squamous Epitheliomas

These grow from the following situations :—

i. **From the skin-surface,** especially about the lips, anus, scrotum, penis, sites of old scars, etc.

ii. **From mucous membranes** covered by **stratified squamous epithelium,** *e.g.*, mouth, pharynx, larynx, œsophagus, vagina and vaginal portion of cervix uteri : or by **transitional squamous epithelium,** which has undergone **metaplasia,** *e.g.*, bladder, ureters and pelvis of kidney.

iii. **From the remains of the obliterated thyroglossal duct, branchial clefts** and other developmental lines of closure, in some primary epitheliomas of the thyroid, from **Hassall's corpuscles** in the thymus, and in connection with some suprasellar cysts and other tumours.

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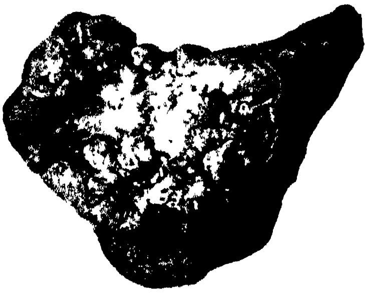
[1] *Acanthoma, see* footnote on p. 337.

The proliferating squamous cells of the skin-epithelium seem capable of growing wherever they can obtain nutriment, *e.g.*, in lymphatics ; and there may be very little connective-tissue formation. As the cells grow, they tend to form layers corresponding more or less with those of skin-epithelium. Towards the central parts of the cellular masses, they may become compressed and flattened, and undergo horny transformation or cornification, giving rise to the so-called " cell-nest " or " epithelial pearl " appearance, the peripheral cells corresponding to the deeper, more actively proliferating, formative layer of epithelium, and the central cells to the ordinary superficial layer—the stratum corneum. Sometimes, however, cornification does not occur to any great extent. As the masses grow, they infiltrate and compress the other tissues ; and they themselves also undergo degeneration very readily. The connective tissue between the masses may be fibro-cellular, and may show leucocyte-infiltration, and often a considerable degree of vascularity. Squamous epitheliomas sometimes arise as the product of a process of metaplasia, as, for instance, when they develop from the mucous membranes of the gall-bladder, bronchi or renal pelvis.



irregular warty - looking tumour, with raised indurated edges.

In the process of infiltration by malignant squamous-celled tumours, the normal relationship of the different layers is reversed, the condition being an invasion of the deeper by the more superficial elements—in contradistinction to what occurs in the outgrowth of a simple squamous papilloma, in which surface structures remain upon the surface, the normal relationship being preserved.

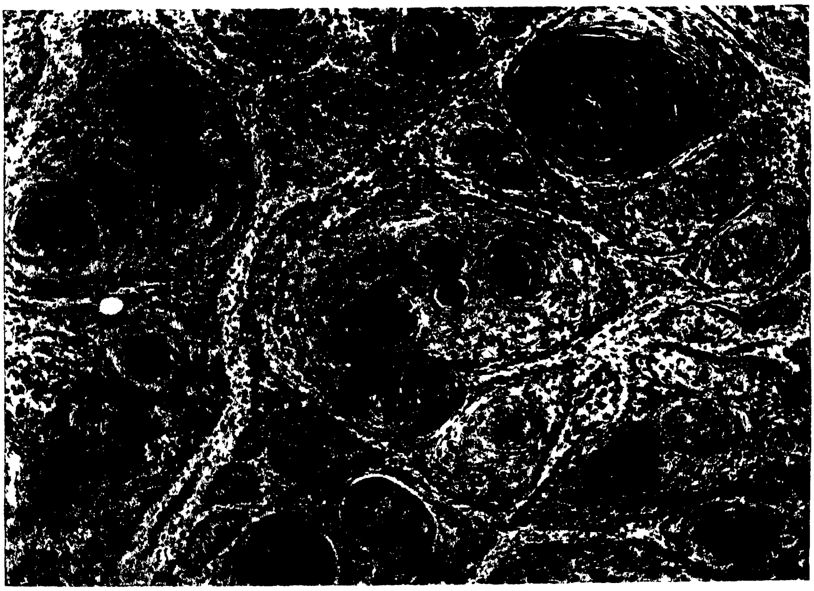
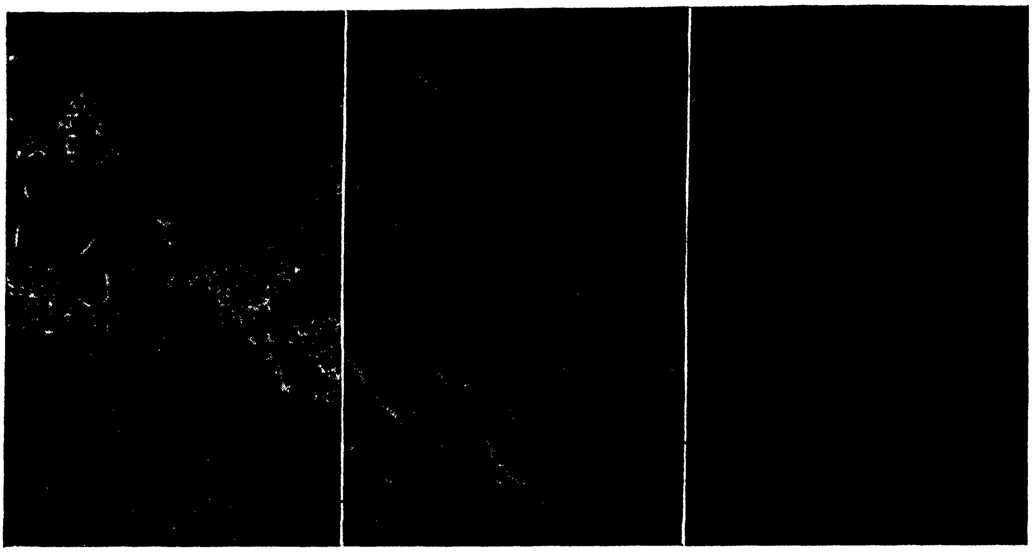


FIG. 167. *Squamous-celled carcinoma of penis*, showing infiltration of the deeper tissues with squamous epithelium, which at parts shows the characteristic " cell-nest " or "epithelial-pearl " arrangement. × 50.



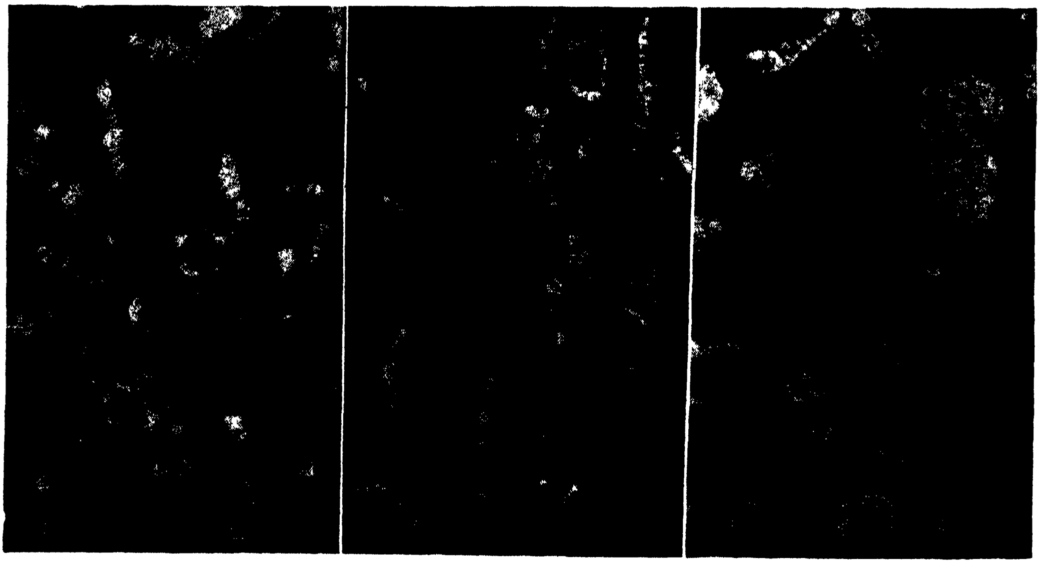
A × 85 B × 85 C × 85

FIG. 168. *Squamous epitheliomata of larynx.* Series of photomicrographs to illustrate *grades of malignancy, infiltration* and *types of tumour-cell.* (Lionel Colledge and Carnegie Dickson.)

A. *A grade*-1 *tumour* from man aged 58, showing well-differentiated whorls of cornified surface-epithelium. Hæmatoxylin and eosin.

B. *A grade*-3 *tumour* from woman aged 63 (*see* Fig. 348x, F, p. 568B, in which cells show pronounced anaplasia, and little or no cell-nest formation). Van Gieson and hæmatoxylin.

C. *A grade*-3 *tumour* from man of 33, retaining prickle-cell formation—*see* E and F below —but with practically no "epithelial pearls." Hæmatoxylin and eosin.



D × 1000 E × 1000 F × 1000

FIG. 169.—*Squamous epitheliomata of larnyx* (*continued*).

D. "*Prickle-cells*" from *non*-neoplastic (syphilitic) patch of *leukoplakia* of vocal fold in man of 58 (*see* Fig. 348x, A, p. 568B). Cells small and *not* anaplastic.

E. *Cells of grade*-3 *acanthoma* from man aged 33 years—*see* C above. Cells show considerable anaplasia, but still retain "prickles."

F. From same case as C and E, showing that *prickles* (note rows of little spindle-shaped swellings on these) *are intercellular continuations of fibrils in cytoplasm of cells.*

(D) to (F) are stained with fuchsin and hæmatoxylin.

Of recent years, the **histological grading of tumours** has received much attention, particularly in America,[1] and of the tumours dealt with in this way the group of squamous epitheliomas illustrates the principle best of all. Such grouping or grading involves the arbitrary division of tumours into four categories according to the degree of differentation shown by their component cells. Especially is account taken of the degree of anaplasia present. the presence or absence of " prickles " [2] (" intercellular bridges ") and cornification, of hyperchromatism of their nuclei and the number of mitotic figures. Thus with **Grade-1** tumours (the least malignant) not more than 25 per cent. (0 to 25 per cent.) of the cells are lacking in well-marked differentiation, the rest showing definite keratinisation and a well-marked degree of tissue-differentiation, **Grade-2** shows from about a quarter up to about half the cells undifferentiated : **Grade-3** from 50 to 75 per cent. of undifferentiated cells : and **Grade-4** (the most malignant) an excess over 75 per cent. of undifferentiated cells which exhibit extreme anaplasia and show numerous mitotic figures.

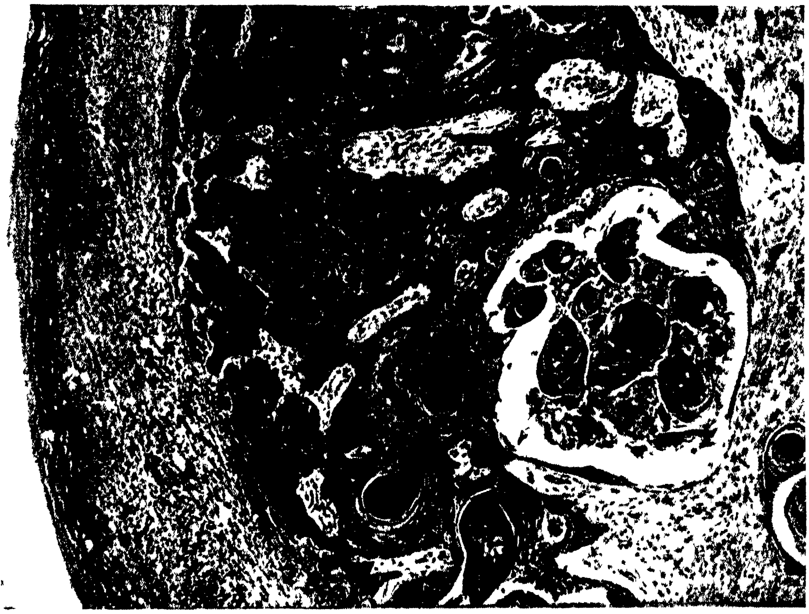


FIG. 170. *Squamous epithelioma.* Secondary nodule in a lymph-node, showing reproduction of characters of the original tumour, including " cell-nests," etc. × 60.

This **grading of malignant neoplasms** involves a useful concept which aids in understanding their behaviour. Its implications must, however, be well understood, otherwise such numerical indices become sources of danger in determining treatment and prognosis. Several points must be kept constantly in mind, namely : that the behaviour of a carcinoma is not always in full accord with its supposed " grade " : that different parts of the same neoplasm may differ greatly in level of differentiation : and particularly that histological grade need not run parallel with the clinical advance of the neoplasm, *e.g.*, a

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[1] " The Grading of Carcinoma," by Albert C. Broders, Mayo Clinic, *Minnesota Medicine*, 1925, **8**, 726.

[2] Squamous-celled tumours in which these " prickles " or intercellular bridges are found between the cells are now often described as " acanthomas," from Greek *ἄκανθα, akantha*, a prickle or thorn, hence the Latin *acanthus*, a prickly tree. See Fig. 169, D, E, and F, opposite.

"Grade-1 carcinoma" when first seen by the clinician may be widespread, with multiple metastases; or conversely a "Grade-4 carcinoma" may come under observation whilst it is a small and still local lesion. Generally speaking, the less well-differentiated neoplasms (Grades 3 and 4) grow more rapidly, metastasise earlier, but are more likely to be radio-sensitive than are those of which a majority of the cells attain a higher level of differentiation.

Similarly, the following **clinical classification** [1] of tumours such as epithelioma of the tongue or larynx (p. 568B) by so-called "**stages**" is useful, but must be accepted under the same reservations :—

Stage I : Small localised primary growth, with *no* involvement of lymph-nodes, and *no* loss of mobility or function.

Stage II : Spread of primary growth beyond tissue of origin, with fixation to neighbouring structures : but still "*no* lymph-nodes."

Stage III : Ditto, but *with* involvement of lymph-nodes.

Stage IV : Extensive advanced cases, with metastases and cachexia—"inoperable."

As we point out when discussing malignant tumours of the breast (pp. 947–8), infiltration of lymphatic channels by a process of "permeation," or in other instances by the embolic passage of tumour-cells by way of their lumina, is likely to have taken place before the involvement of the nodes into which they drain—a phenomenon demonstrable, perhaps, only by extensive and careful microscopical investigation of the intervening tissues. In other cases, *e.g.*, of carcinoma of the stomach, lymph-nodes at a distance, and not necessarily the nearest groups, may become involved (p. 730). In this connection, Figs. 349 (A), (B) and (E) on pp. 570–1, and Fig. 351 on p. 573 will repay careful study.

BASAL-CELLED CARCINOMA and RODENT ULCER.[2] A distinction has sometimes been drawn between these, but the present-day view is that they are to be regarded rather as variants or even as practically identical tumours, both derived from the deeper or formative layer of the squamous epithelium of the skin. It has been said that the "basal-celled carcinoma" shows little or no tendency to undergo ulceration; whilst the characteristic of the "rodent," as implied by its name, is that it slowly undergoes progressive ulceration, a process which, however, may perhaps not commence for several, or even for many, years after the first appearance of the nodule. This is situated most frequently in the skin of the face, for example about the junction of the nose with the cheek, or at the outer canthus of the eye. Norman Walker and Percival describe the nodule as having at first "a glistening, translucent appearance, comparable to that of the horn of a light-coloured cow," and at this stage it may remain for a period even of years. In the case of the typical rodent ulcer, the lesion, unless suitably treated, *e.g.*, with radium, may then at any time proceed to grow and spread, with the formation of the characteristic ridge-like elevated margin—the so-called "rolled edge"—the central area becoming first flattened down and then ulcerating to form the characteristic lake-like hollow or crater, which gradually eats its way into the subjacent and surrounding tissues. Histologically, it has a certain resemblance in structure to the ordinary squamous-celled epithelioma. Irregular whorls or papilliform processes of epithelial cells pass downwards in various directions through the cutis vera and subcutaneous tissues (Fig. 171 below, and 171A in Appendix, p. 1255; but the cells are usually smaller than those of the ordinary acanthoma and do not, as a rule, show any development of " prickles " ; nor are they so clearly separated into layers, and there is little or no tendency to any cornification or the formation of " cell-nests." The cells stain deeply, and in the more central parts are closely packed and irregularly polygonal, but at the periphery are larger and more cylindrical in shape, thus resembling the cells of the basal or formative layer of the stratum Malpighii from which, as noted above, they in all probability arise, though they can also originate from the epithelium of sebaceous or sweat-glands or of hair-follicles. We have ourselves traced the origin of some squamous-celled epitheliomas, *e.g.*, of the larynx, to the " basal " or outer layers of the mucous-gland ducts, especially towards their exits ; and we have noted in these, as well as in squamous-celled epitheliomas originating from the lips and elsewhere, an occasional tendency for the proliferating basal epithelial cells to assume a spindle-celled morphology, as was originally described by E. Krompecher [1] in 1900—a metastasis which accounts for their sometimes having been mistaken for a " transformation into spindle-celled sarcomas."

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[1] Modified from *Five-Year Statistical Report* of the Christie Hospital and Radium Institute, 1939 : quoted by Sir Alfred Webb-Johnson, *Brit. Med. Jour.*, 1941, i, 5. (Under "Stage I," a measurement of "not more than 3 cm. in greatest diameter" is given in the original, but this figure we think is too large for this early stage.)

[2] For clinical descriptions of this and other skin-lesions, see Norman Walker and G. H. Percival's "Introduction to Dermatology," tenth edition, 1939. W. Green & Son Ltd., Edinburgh, p. 337.

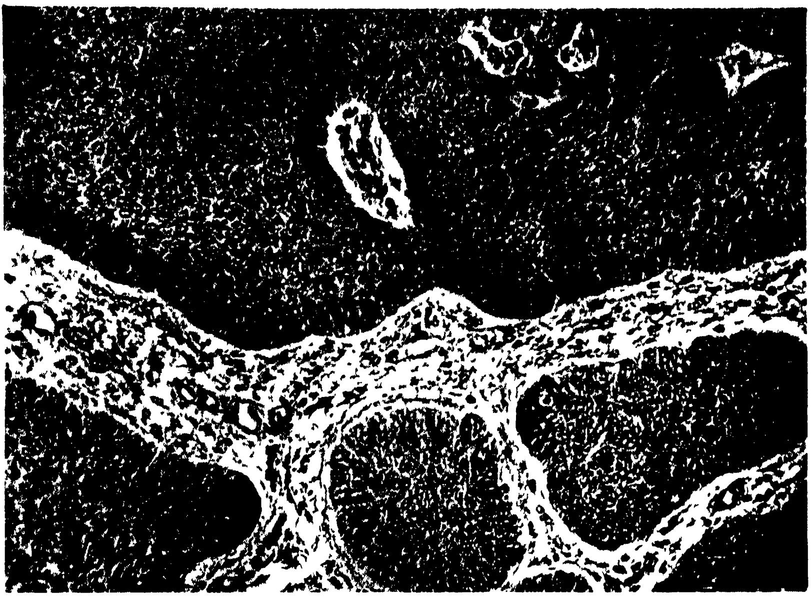

FIG. 171. *Rodent ulcer.* High-power view, showing character and arrangement of the epithelial cells (*see* text). × 200.

Lympho-epithelioma. This somewhat ill-defined variety of tumour develops occasionally from the surface layers of the tonsils and lymphoid tissue of the naso-pharynx and tongue. It is produced by a combined proliferation of surface epithelium and subjacent lymphoid tissue, and may infiltrate the surrounding structures and give rise to metastases in neighbouring lymph-nodes and elsewhere. It is radio-sensitive, but, owing to its tendency to diffusion, the ultimate prognosis is unfavourable.

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[1] *Beiträge zur patholog. Anat. und allgem. Pathol.*, 1900, **28**, 1 and 1905, **37**, 28.

(*b*) Glandular Carcinomas or Glandular Cancers

The various glands of the body may be divided roughly into groups in which the epithelium is arranged in :—

i. **Ducts, tubules and acini** : salivary or mucous glands, breast, etc.
ii. **Cyst-like spaces** : the thyroid.
iii. **Solid masses, columns, etc.** : the suprarenal cortex, etc.
iv. **Intermediate and combined forms** :—
  Cell-masses or columns *plus* **ducts** : liver, sebaceous glands, etc.
  Ducts, tubules and acini *plus* **solid "islands" of interstitial cells** : pancreas, testicle, etc.

The **lung,** though a complex structure, might be included with the first sub-group, since the bronchi may be likened to ducts and the alveoli to acini; whilst in addition tumours may arise also from the bronchial mucous glands or lymphoid tissue.

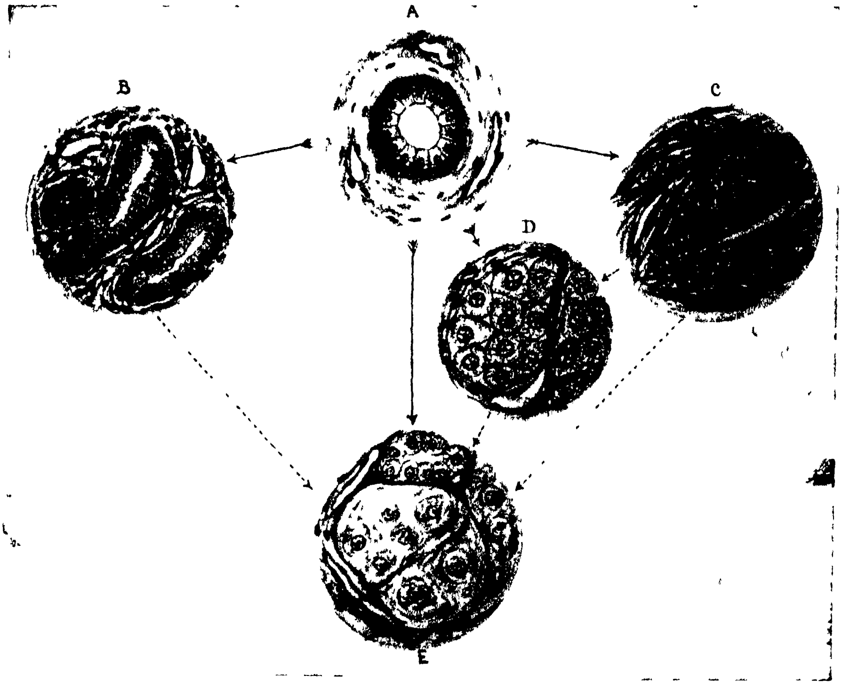


FIG. 172. Schematic representation of the *varieties of carcinoma which may arise from the epithelium of a tubular gland.*

A. Transverse section of *Normal Gland-Acinus* consisting of regular epithelium upon a basement-membrane, surrounded by a connective-tissue stroma containing nutrient vessels. This may give rise to any of the following types of new growth:
B. *Malignant Adenoma* or *Adeno-carcinoma*, with irregularity in shape of acini, the lumen of which persists. Absence of basement-membrane. Irritation, giving rise to proliferative overgrowth, and increased cellularity of stroma.
C. *Scirrhous* or *Hard Cancer,* in which solid clumps of cells are formed, and which by their irritation give rise to dense fibrous-tissue overgrowth.
D. *Encephaloid, Medullary* or *Soft Cancer,* which may arise directly, or may supervene upon the harder variety, the two resembling one another in being composed of solid clumps of epithelial cells.
E. *Mucinoid* or *"Colloid" Cancer,* which may arise directly from the normal gland-type, or may supervene upon any of the other forms.

The particular structural element of a glandular organ or tissue from which a given tumour has arisen may sometimes be determined by noting the reproduction in the tumour, perhaps more or less imperfectly, of any of the histological characters of the original organ or tissue. In other instances, however, the deviation is so extreme that the original type of gland-structure may be obscured or perhaps completely lost. In order to study these phenomena, it is convenient to take as an example the ordinary acinar gland, and to consider the changes which may occur in the tumours which grow from it. These tumours may retain some of the general glandular arrangement, *e.g.*, acinar or duct-like spaces, as in malignant adenoma or adeno-carcinoma ; or the cells may form solid masses among the fibrous tissue, without definite arrangement, as in the spheroidal-celled scirrhous and encephaloid varieties ; or they may show abnormalities in size, structure, etc., as in encephaloid cancer : or degenerative changes, as in mucinoid or " colloid " cancer (Fig. 172, opposite).

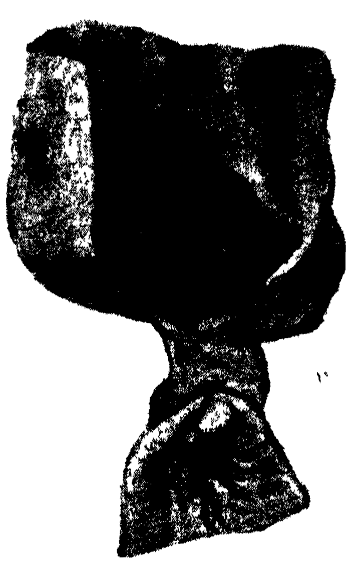


Fig. 173. *Malignant adenoma of the large intestine* producing great narrowing—the so-called "*Malignant Stricture.*" Note dilatation, hypertrophy and ulceration above, and atrophy below, the seat of stricture.

VARIETIES OF GLANDULAR CANCER

1. COLUMNAR-CELLED CARCINOMA, MALIGNANT ADENOMA, or ADENO-CARCINOMA (also called **Adenoid Cancer, Duct-Cancer, Columnar-celled Epithelioma**), in which the general glandular arrangement of the epithelium in acinar spaces, etc., is preserved. In malignant adenomas arising from glandular organs which do not possess a tubular structure (*e.g.*, the liver—apart from the bile-ducts), the arrangement of epithelium characteristic of the organ may be reproduced, usually in a more or less aberrant fashion.

Sites. The large intestine and stomach : the uterine mucous membrane : the bile-ducts : the ducts and acini of glands such as the breast, salivary glands, pancreas, and many others.

Microscopical Structure. The cells are arranged in alveoli or tubes, generally very irregular in shape and size, lined by columnar, or in some cases cubical, epithelium—arranged usually in a single layer, though several, and in some instances many, layers may develop. In some malignant adenomas, certain of the acini may give rise to cystic dilatations, and these in turn may show papillomatous ingrowths. The stroma, as a rule, consists of delicate connective tissue, which is often highly cellular, and may exhibit the variations and degenerative changes common to all cancers.

The histological distinctions between malignant and simple adenomas are often difficult to determine and only relative. In malignant types, there is usually (i) infiltration at the margins, and absence of a definite capsule:

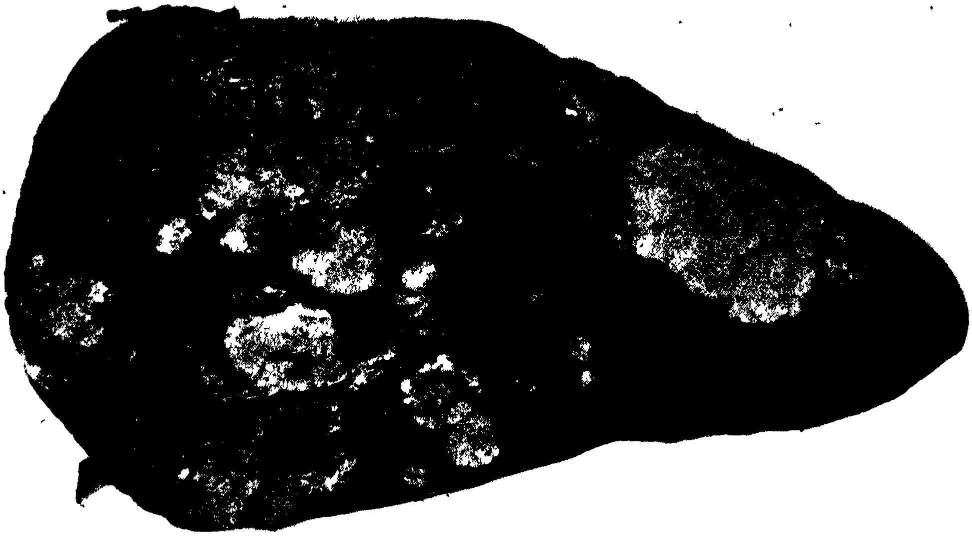


FIG. 174. *Primary malignant adenoma of liver, hepatoma* or "*liver-celled cancer,*" in which the epithelial cells (as shown in the subjacent Fig. 175) are arranged in irregular columns resembling those of the liver itself.

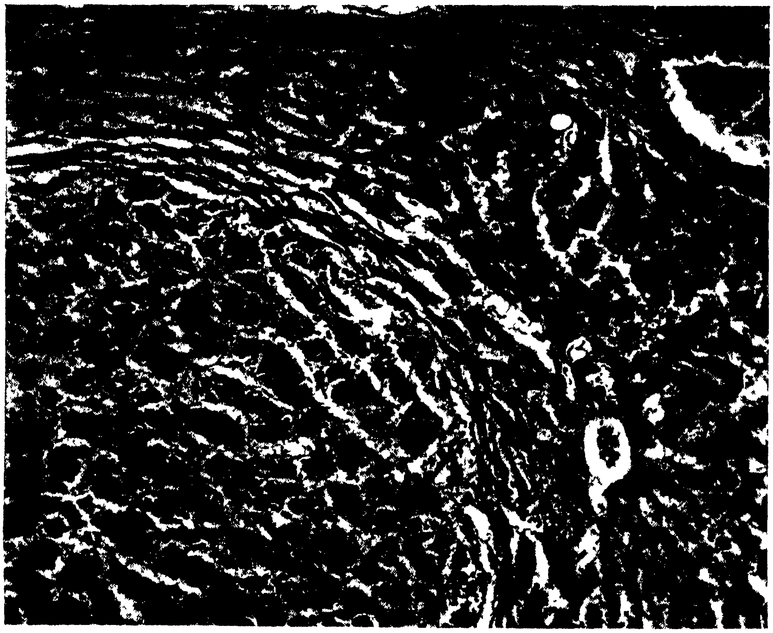


FIG 175. *Primary liver-celled carcinoma*, showing (below and to the left) irregular columns of large cells, resembling those of the liver, but with aberrations in size, appearance of the nucleus, etc. The cells of the surrounding liver-tissue are undergoing compression-atrophy. × 100.

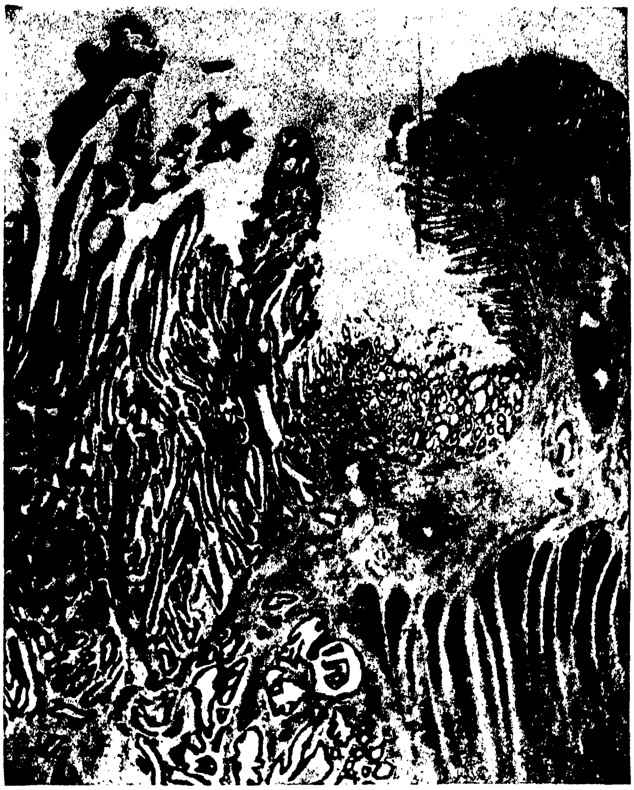
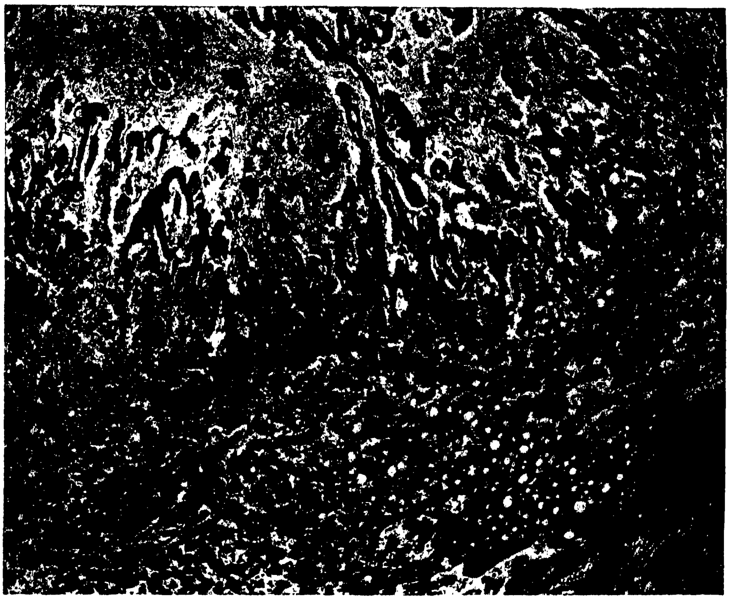


FIG. 176. *Malignant adenoma.* Primary growth in large intestine. Towards the right are seen the normal mucous, submucous, and muscular coats of the bowel. Towards the left are the large, irregular tube-like acini of the new growth, lined by large dark-staining columnar epithelium. Infiltration of the submucous and muscular coats at the spreading margin is seen. × 10.



177. *Malignant adenoma.* A secondary nodule in the liver (reproducing the irregularly tubular character of the primary growth which was in large intestine). Shows infiltration of normal tissues at margin and absence of capsulation. The liver-tissue (in the lower part of the section) shows some fatty infiltration. × 50.

(ii) deficiency or complete absence of the basement-membrane: and (iii) evidence of increased activity in cell-division, and greater aberrations in the size and shape of the cells and cell-groups. The acini are often larger than they are in simple adenomas, and tend to be elongated and distorted (Fig. 172, B), boring their way, as it were, along the lymphatic spaces, and between the other tissue-elements.

2. **SPHEROIDAL-CELLED SCIRRHOUS CARCINOMA, "HARD CANCER" or SCIRRHUS.**[1] The density of these tumours is due to the slowness of their growth and the irritation in the surrounding tissues produced by the cells, with the consequent production of a dense fibrous-tissue stroma (Figs. 178 to 185).

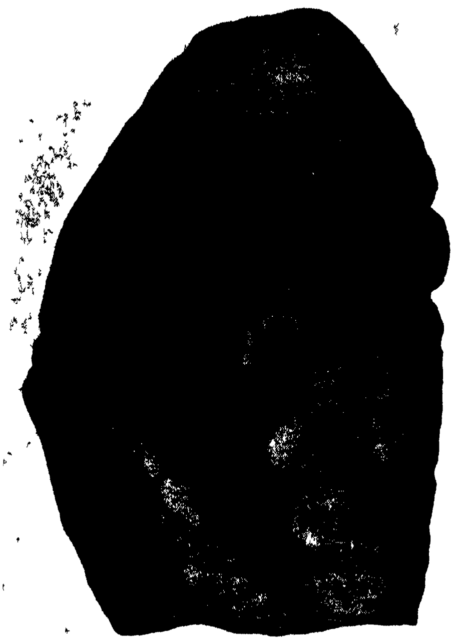


FIG. 178. *Scirrhous carcinoma of breast.* Naked-eye photograph showing the characteristic retraction of the nipple and the spread of the (darker) tumour-tissue backward amongst the (lighter) fatty tissue into the deeper part of the organ.

Sites. These hard tumours are especially common in the mammary gland, and are found also in the stomach, large intestine, ovary and prostate.

Microscopical Structure. The cells lose their acinar arrangement, and are found in solid masses or clumps, varying greatly in size and shape, and surrounded by a dense fibrous-tissue stroma, which may resemble that of cicatricial tissue, with perhaps here and there somewhat more cellular areas and areas showing "small-celled infiltration" with lymphocyte-like cells. Occasionally, there may be an abortive attempt at the formation of a lumen in some of the cell-masses. In individual tumours, *e.g.*, in those occurring in the breast, the condition of scirrhous cancer seems to supervene in certain cases of so-called "chronic fibroid mastitis," "adenosis" and "fibro-adenoma," but opinion differs as to whether this is the result of a true transition or not. Appearances can be found readily to support the view of malignant transformation, but the point is unlikely to be finally settled until the true ætiology of malignant conditions of the breast is understood. Frequently, also, in a single specimen, different areas may exhibit the varied characters of malignant adenomatous, scirrhous and encephaloid types of cancer.

Ewing, in his well-known book on tumours[2] (1940), states that: "In chronic mastitis single small cancer nodules may appear," and he believes that

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[1] *Greek*, *σκῖρος* or *σκίρρος*, *skīros* or *skirrhos*, any hard covering, hence a hard swelling or tumour, *Latin*, *scirrhus*. The English derivatives are the substantive "scirrhus", the hard mass itself, and the adjective "scirrhous," as in a "scirrhous tumour." (Note the double *ρ* in the middle of a Greek word is equivalent to *ῤῥ* *i.e.*, *r rh*, as also in hæmo-rrhage.)

[2] "Neoplastic Diseases: A Treatise on Tumors," by James Ewing, Cornell University Medical College, New York City, 4th ed., 1940, p. 19.

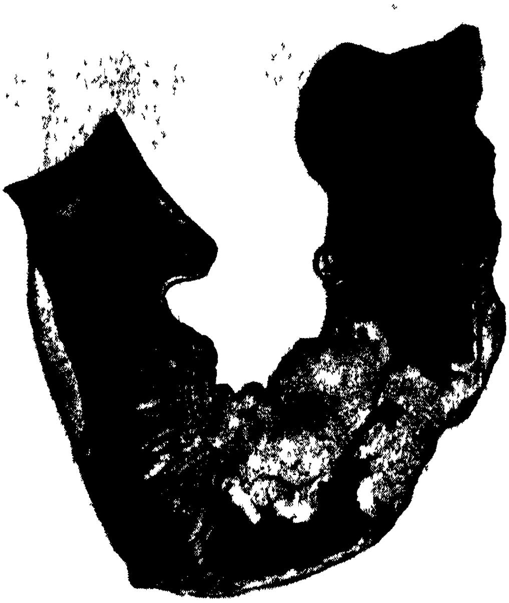

FIG. 179. "*Hard cancer*" *or scirrhus of intestine*, producing almost complete obstruction of lumen.

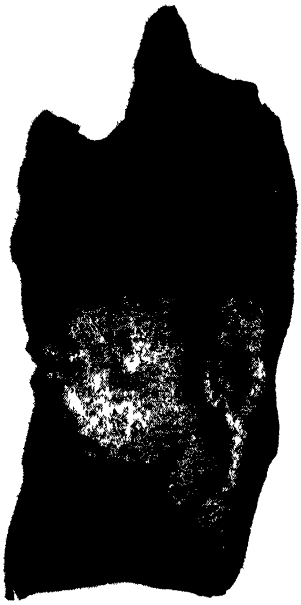

FIG. 180. A similar malignant "string-stricture" of the intestine caused by a *malignant adenoma* or *adeno-carcinoma* (p. 341).

" their preliminary stages may be traced in other portions of the breast, chiefly in the ducts. Here one finds hyperplasia of lining cells. . . . Yet other cells show more active proliferation, increase in size and in nuclear chromatin ;

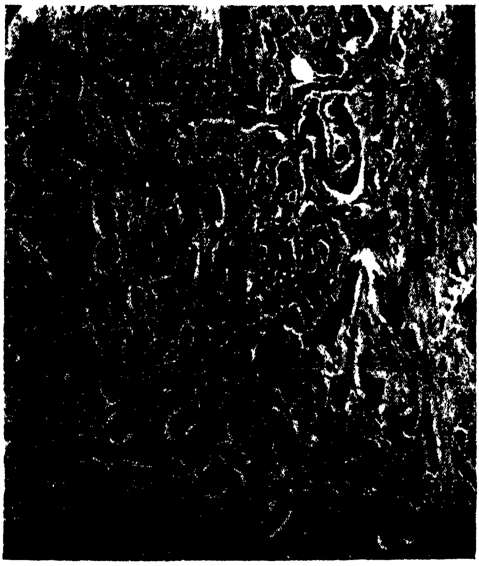

FIG. 181. *Scirrhous carcinoma of breast:* spreading edge of tumour, showing the clumps of cells amongst dense fibrous tissue. Hæmatoxylin and eosin. × 75.

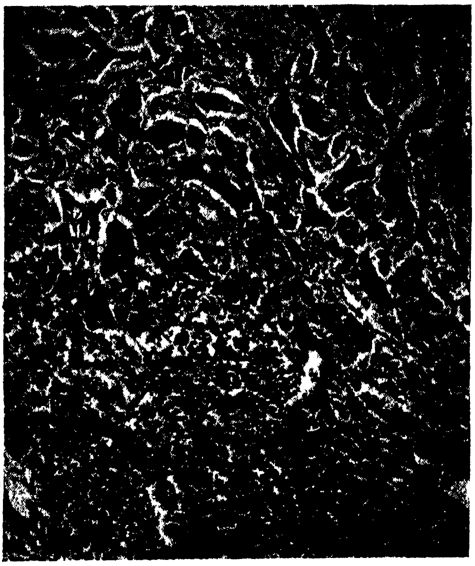

FIG. 182. *Scirrhous carcinoma of breast:* spread to an axillary lymph-node. Hæmatoxylin and eosin. × 75.

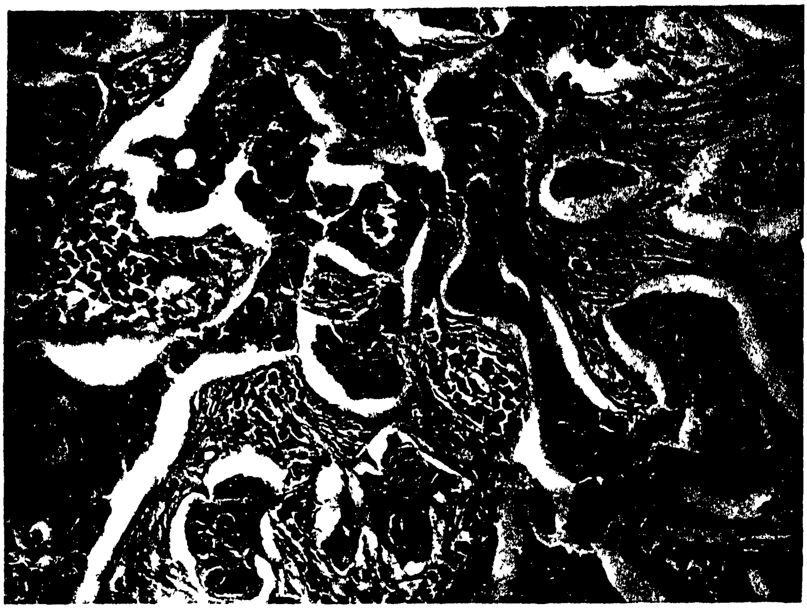

FIG. 183. *Scirrhous carcinoma of breast,* showing solid masses of cells amongst dense fibrous tissue. (The clear spaces are artefacts due to shrinking and retraction during paraffin-embedding.) × 200.

. . . and it is possible to trace such cells into types closely approaching those seen in early carcinoma." Similarly, Sir Robert Muir, of Glasgow, writes [1]: "My experience is that in the great majority of cases of carcinoma a lesion of this

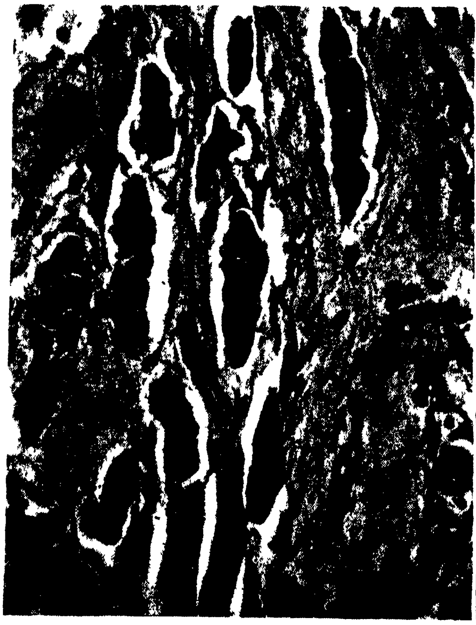

FIG. 184. *Scirrhous carcinoma of breast:* Elongated clumps of malignant cells infiltrating along the tissue-spaces and producing the characteristic fibrous-tissue proliferative reaction.

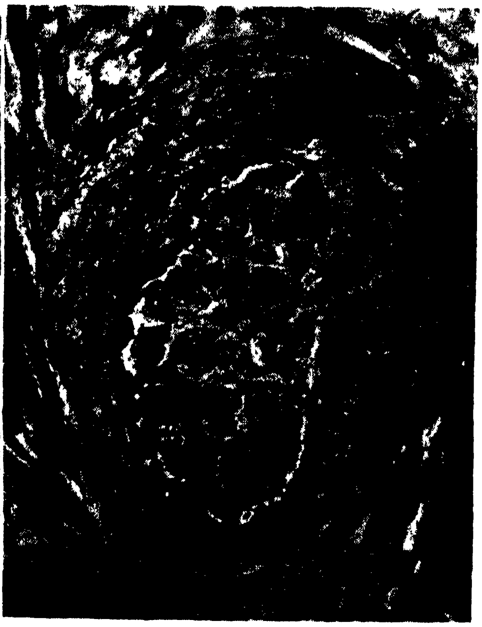

FIG. 185. A plug of malignant cells in a thickened lymphatic vessel draining into the axilla. Hæmatoxylin and eosin. × 300.

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[1] "Text-Book of Pathology," by Sir Robert Muir, 4th ed., 1936, pp. 912 and 916.

kind [localised hyperplastic disease] can be found as a pre-existing condition ; . . . and the main changes are forms of epithelial hyperplasia, terminating not infrequently in intraduct carcinoma." . . . "We believe that in the large majority of cases it [carcinoma] is preceded by the hyperplastic changes in the ducts and acini . . . the extreme of which is intraduct carcinoma." In a subsequent paper,[1] Muir (1941) confirms and convincingly illustrates his view that carcinoma of the breast can originate either **in the ducts** or **in the glandular acini** of the organ, though more frequently in the former than in the latter ; and, moreover, he traces all stages, from the hormone-stimulated **pre-cancerous hyperplasia** and **transformation into,** and the definite **onset and development of, malignancy**—frequently in multiple foci, but sometimes more diffuse or regional. He finds *no* histological evidence that two distinct causal factors (such as hormone *plus* virus) are concerned with the production of the appearances which he describes ; and he regards the hyperplastic and neoplastic changes as stages in one continuous process which together "represent the effect of one growth stimulus . . . of the nature of a widely acting chemical substance such as a hormone rather than a particulate agent such as a virus" —a conclusion which has certain analogies with that of Joseph Needham (p. 291 *et seq.*) with reference to his work in experimental embryology, though expressed in a different form and in another connection. The observations of one of the authors of this text-book (W. E. C. D.) [2] on the onset and development of mammary cancer are in entire agreement with those of Sir Robert Muir, and our present attitude to this particular problem of carcinogenesis is well summed up by the Editor of the *British Medical Journal* in his "Annotation" [3] : "The implication of his (Sir Robert Muir's) remarks will doubtless have an influence on medical teaching, so that the student will be taught to regard the focal origin of mammary cancer not as a scientific fact but merely as an approximation to reality and as a gross but serviceable guide to the operator."

3. **SPHEROIDAL-CELLED ENCEPHALOID CARCINOMA, MEDULLARY or "SOFT CANCER."** [4] In this variety of tumour, growth is more rapid, but it must be understood clearly that no hard and fast line of distinction can be drawn between the so-called "scirrhous" and "encephaloid" varieties, and that intermediate forms are common.

Sites. These softer tumours are found especially at or near the cardiac end of the stomach and elsewhere in the digestive tract, in the breast, pancreas, liver, and other glandular organs.

Microscopical Structure. In general structure, these encephaloid growths resemble scirrhous cancers, but the cell-groups tend to be considerably larger, and the cells usually show great variety in shape and size, being often large, and exhibiting a pronounced tendency to degeneration. Cell-proliferation in these

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[1] "The Evolution of Carcinoma of the Mamma," by Sir Robert Muir, Glasgow, *Jour. Path. and Bact.*, 1941, **52**, 155.

[2] Based upon the experience of many years work on material from the Grosvenor Hospital for Women and other hospitals, in collaboration with the late Dr. R. A. Gibbons and Sir Henry Simson.

[3] "The Focal Origin of Mammary Cancer," "Annotation," *Brit. Med. Jour.*, 1941, **i**, 423.

[4] The terms "encephaloid" and "medullary" are used here merely to signify "soft," like brain-tissue or marrow in consistence—in contradistinction to "scirrhous," "hard."

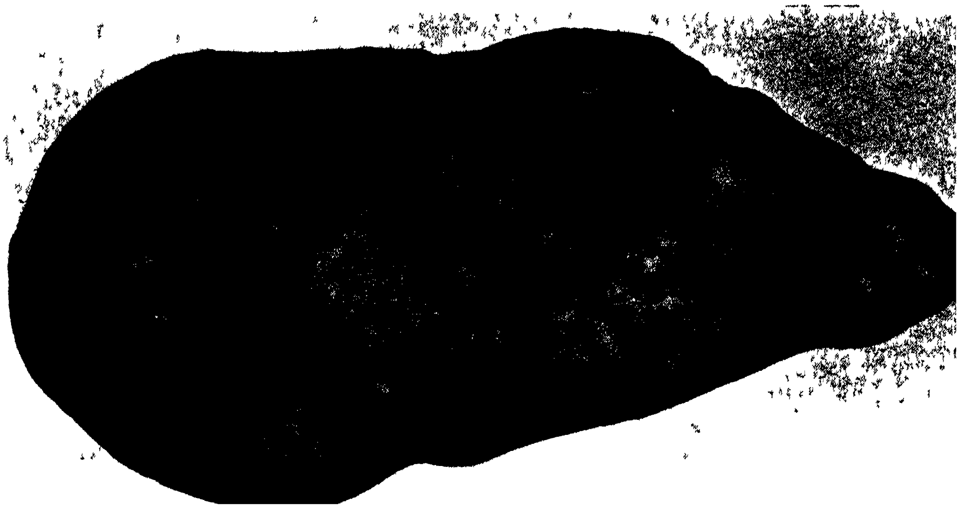


FIG. 186 *Encephaloid carcinoma : metastases in liver* from a primary grow in the breast

neoplasms is usually very rapid, and numerous mitotic figures are frequentl to be observed, especially at the spreading edges. These mitotic figures ar sometimes abnormal in character, and may show, for example, multipola division, inequality in the number of chromosomes in the daughter-nuclei, etc

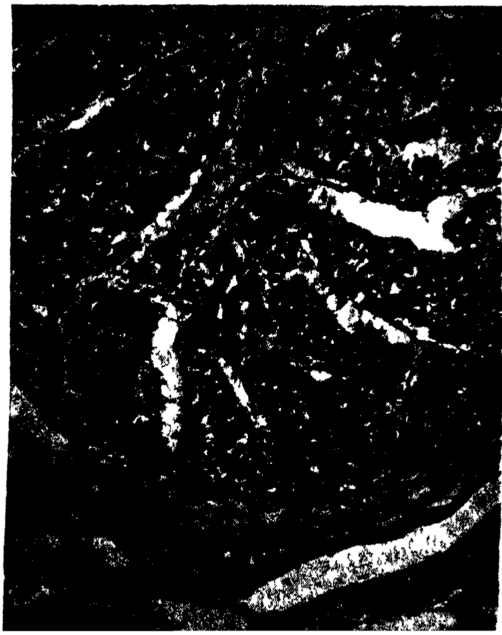


FIG. 187. *Encephaloid Carcinoma or "Soft Cancer" of Breast.* Low-power view to show looser arrangement and scantier fibrous-tissue framework than in scirrhous tumours. Hæmatoxylin and eosin. × 85

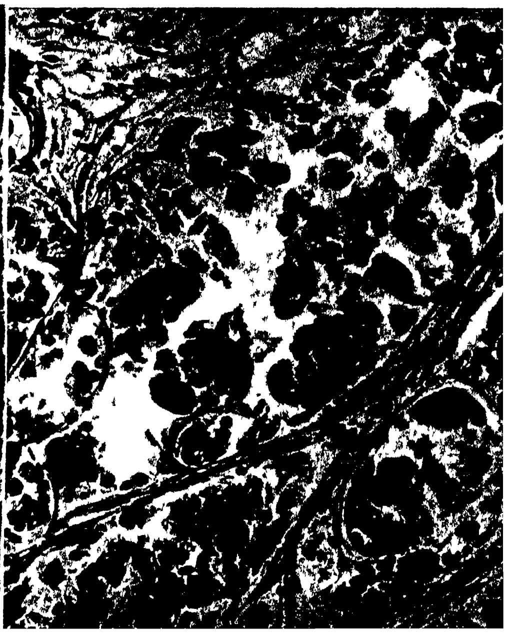


FIG. 188. *High-power view of a similar specimen,* showing irregular character and loose arrangement of the tumour-cells, and scanty fibrous-tissue framework. Hæmatoxylin and eosin. × 200

(p. 9: and Figs. 127 and 128, p. 276). The tumour-cells are often actively phagocytic, and may englobe leucocytes, red blood-corpuscles and other cells in great numbers (Figs. 126 and 740, pp. 271 and 1150).

As noted above, in the section on scirrhous cancer, all intermediate degrees between hard and soft cancers are found. In an individual tumour, variations in consistence may also occur in different areas; and, not infrequently, the secondary growths derived from a scirrhus may produce distinctly softer growths in other organs and tissues. Similarly, an admixture of these forms and malignant adenoma may occur.

4 **MUCINOID or "COLLOID" CANCER** is so named from the tendency of the cells to undergo rapid "colloid" degeneration. The majority of these degenerative processes are, however, really **mucinoid** in type, though the term "colloid" remains in common use. We use the term "colloid" here with no specific chemical significance, but merely as descriptive of the physical character and consistence of the tissue, as the word itself means glue-like or jelly-like (p. 203).

Sites. The stomach, intestines, mammary gland, and other situations in which encephaloid cancers and malignant adenomas are found constitute the important sites of origin. Widespread secondary involvement of the peritoneum or pleura may occur. Bilateral secondary involvement of the ovaries is found in the so-called "Krukenberg tumour" (pp. 730 and 929–30).

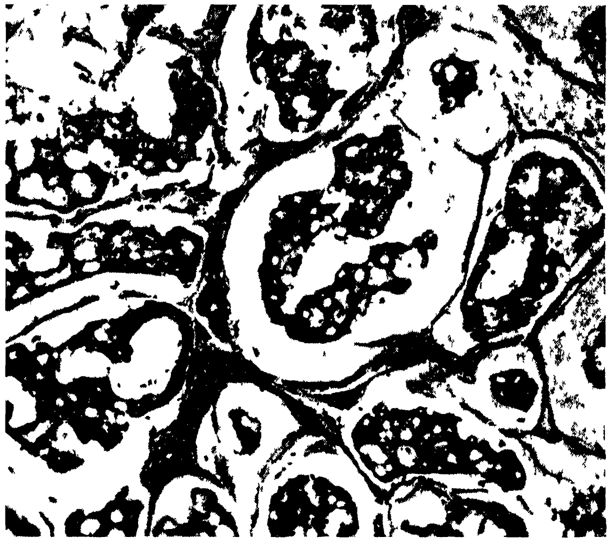


FIG. 189. *Mucinoid ("colloid") Carcinoma of the Breast.* × 80.

Microscopical Structure. Mucinoid degeneration may supervene in any of the other types of cancer, especially the encephaloid and some of the malignant adenomatous varieties (Fig. 189; *cf.* also Fig. 172, E, p. 340). The structure, therefore, depends largely upon the nature of the original tumour in which the change has occurred, though, in some cases, the process of mucinoid transformation is present from the first, or at all events, may supervene early. Mucinoid cancers usually show large spaces lined by a layer of cells undergoing the mucinoid change; or the degenerating cells may be scattered irregularly throughout the mucinoid material filling the spaces. These spaces are formed in the loose, often œdematous, connective tissue, and contain the mucinoid material formed by the breaking-down of the epithelial cells, the degenerating remains of which may usually be seen scattered among it.

Discrimination should be maintained between **carcinoma myxomatosum** in which the mucinoid change is due to degeneration of the stroma, and **carcinoma**

mucosum in which the mucin is a product of the carcinoma-cells themselves. This latter is the form to which the term " colloid " carcinoma is still not infrequently applied, and in which characteristic " signet-ring " cells are usually seen. These are carcinoma-cells containing a single large globule of mucin which displaces the nucleus to the periphery of the cell, producing an appearance resembling that of the " vacuoles " characteristic of the " physaliphorous cells " of Virchow in chordomas (Fig. 141, p. 307). In certain tumours, *e.g.*, metastases from bronchial carcinomas, **mucin may be secreted** by the tumour-cells, which may imperfectly retain and reproduce the mucin-secreting capacity of the cells from which they have originated (p. 573 : Fig. 351, p. 573 : and Figs. 733–5, pp. 1146–7).

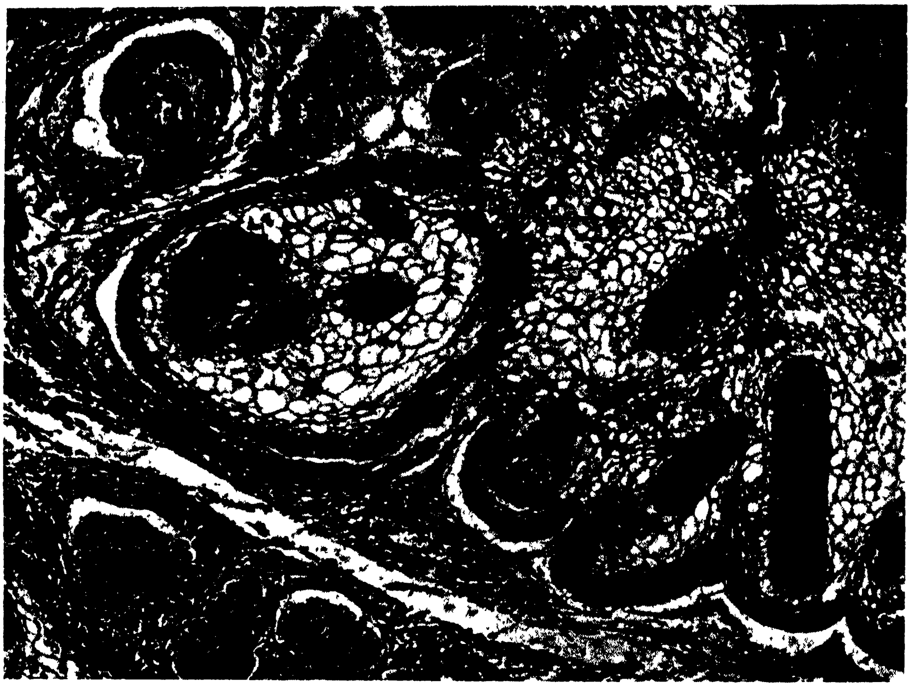


FIG. 190. *Adamantinoma*, from a suprasellar cystic tumour in a boy aged 15 years. (From the W. E. H. case illustrated in Fig. 472, p. 817.) Van Gieson and hæmatoxylin. × 100.

" HYPERNEPHROMAS." These are described under tumours of the kidney (p. 895), as there is little doubt that the majority of the neoplasms described in the past under this title have been carcinomas of that organ.

CHORIONEPITHELIOMAS. This type of tumour is discussed in the section dealing with the uterus (p. 924) and receives further notice in the next section of this chapter—that devoted to the teratomas (p. 352).

ADAMANTINOMAS. These are a comparatively rare form of epithelial tumour arising in the jaw from the developmental enamel-organ, as one variety of odontome (pp. 308 and 707). Usually benign, they sometimes invade the surrounding tissues and show malignancy by giving rise to metastases. **Suprasellar adamantinomas** (Fig. 190) also occur as intracranial tumours (Figs. 472–3, pp. 817-18).

B. TERATOMAS

(Including Placentomas and Teratoid Tumours)

The term " teratoma " is applied to a mixed tumour which may include in its structure tissues derived from all three of the primitive germinal layers (epiblast, mesoblast and hypoblast). The actual arrangement of the various tissues in these tumours varies indefinitely in individual examples. Sometimes the arrangement is orderly and represents comparatively well-defined types of adult or mature tissue, whilst in other instances the structure of the teratoma is almost entirely one of undifferentiated cells which are deficient in any orderly arrangement such as is associated with properly developed and fully mature tissues. In these less differentiated tumours, malignancy may supervene.

The method of origin of such neoplasms is not yet definitely known. At one time they were considered as tumours arising from the inclusion and continued development of one individual (or the germ-cell or the products of the germ-cell from which that individual would in ordinary circumstances have been developed) within the tissues of another individual of the same species. Another view of the origin of such tumours was that development of the tumour took place from one of the early cells originating from the preliminary proliferation of an ovum and included within the developing somatic tissues of the individual derived from that self-same ovum. The more recent work in Experimental or Inductive Embryology (p. 291) suggests the possibility that such abnormalities as teratomas and teratoid tumours may be " induced " in the body of the individual itself during embryonic or fœtal development (*see* Figs. 129–130, p. 292).

These tumours vary, from the teratomatous " dermoid cyst " composed of little more than ectodermic structures, *e.g.*, skin-epithelium, sebaceous and sweat-glands, hair and teeth, to, in other cases, complex tumours containing, in addition to the foregoing structures, bones, cartilage, muscle, nerves, and even rudimentary viscera, up to the *fœtus in fœtu* of Meckel.

It is probable that the type of tumour to be formed depends, as far as its complexity is concerned, upon whether the origin of the tumour is from toti-potential cells (that is to say, the cells of the blastomere itself) : from multi-potential cells (as from primitive cells of a stage later than the blastomere) : or from uni-potential cells (of the primitive-tissue order).

The commoner teratomatous tumours arise in the ovary and testicle and are described in the sections which deal with these organs (pp. 908–911 and 929). Such tumours may be of either simple or malignant character and exhibit appearances which differ according to their origin and nature.

TERATOID TUMOURS. Along with the above may be taken certain **mixed tumours** arising from inclusions of still imperfectly differentiated portions of the same embryo (*e.g.*, developmental segments, or portions of segments, such as the so-called " myotomes," etc., derived from the developing and differentiating mesoblast) in abnormal situations. This is a possible explanation of the mixed cartilaginous tumours (chondro-sarcoma, myxo-chondro-adenoma, etc.) occurring in the parotid and submaxillary glands, kidney and other portions of the genito-urinary system, and elsewhere. Such tumours may contain, not only cartilage and gland-like tissue, but also bone and muscle.

PLACENTOMA, CHORIONEPITHELIOMA, SYNCYTIOMA or DECIDUOMA MALIGNUM or CHORIONIC CARCINOMA (p. 924). One type of teratomatous tumour of special interest, since it is different in its characters from every other known form of neoplasm, is the **chorionepithelioma,** which originates definitely in the cells of another individual of the same species, the fœtus—in the chorionic tissues of the placenta during or after gestation—and is therefore to be considered a teratoma. Nevertheless, this tumour consists of cellular elements only, and not of formed and organised tissues, so that it can be classed equally well with the cellular tumours or cytomas which have been discussed in the earlier part of this chapter. It is thus a form of tumour which stands alone, in that it is derived from the fœtal syncytial layer of the placenta which proliferates and invades the tissues of the mother. There is also proliferation of the smaller cells from the epithelial covering of the chorionic villi (Langhans' cells). Syncytioma malignum may supervene at the placental site after either a full-time pregnancy or an abortion, or, in most cases, after the expulsion of a "hydatidiform mole." In rare instances, the seat of the tumour may be the uterine (Fallopian) tube, ovary, vagina, and even the labium. In the two first-mentioned sites, the condition has probably followed extra-uterine gestation ; in the last two positions, implantation of the placental cells has probably

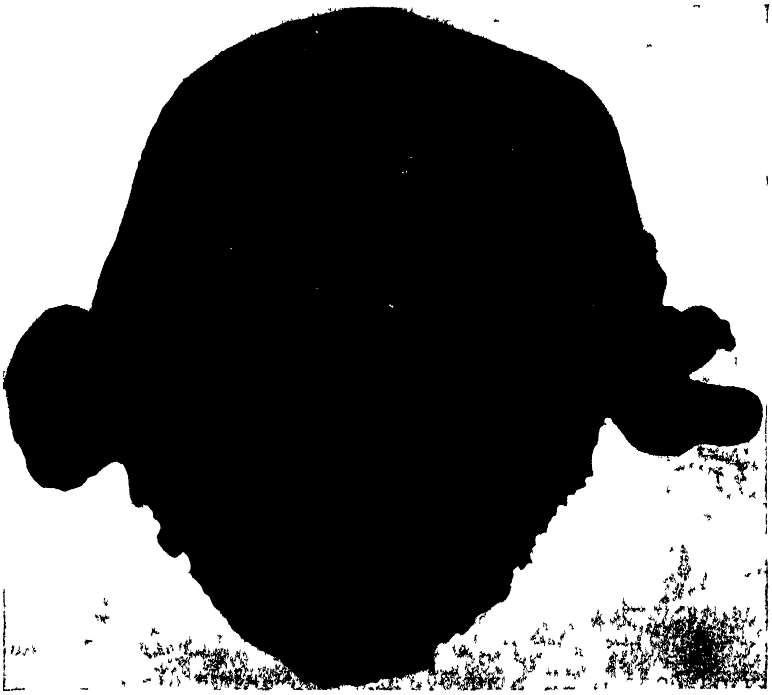


FIG. 191. *Chorionepithelioma Simplex or " Hydatidiform Mole " in situ,* in uterus. There is also seen in section in this specimen a small leiomyoma embedded in the muscular wall, towards the fundus.

taken place. Before regarding such tumours as primary, however, not only the interior, but the muscular wall, of the uterus must be carefully searched, as the primary focus is sometimes situated in it at a distance from the mucous membrane. The tumour grows rapidly—forming irregular, soft, spongy, extremely vascular masses, which readily break down and give rise to hæmorrhages. It is highly malignant, and not only invades the walls of the uterus and uterine (Fallopian) tubes locally, but gives rise to numerous metastases in distant parts, *e.g.*, in the lungs, liver and kidney, the spread being usually embolic, and due to the invasion of the uterine veins. When the secondary growths, *e.g.*, in the liver (p. 783), are examined microscopically, the proliferating tumour-cells of the embolus are not infrequently found within the vessels or penetrating their walls. A few cases have been described in which no primary growth could be found in the uterus or tubes, the secondary growths arising in these cases from perhaps even a single syncytial cell or from small groups of these which have become broken off and disseminated by blood-vessels or by lymphatics. Microscopically, two classes of cell are seen, irregularly intermingled with one another in varying proportions in different examples and invading the tissues of the organ in which the tumour is growing. These are :—(1) large, irregular, plasmodial masses derived from the syncytium, sometimes multinucleated, in other instances with a definite cell-outline and a single nucleus : and (2) groups of small polyhedral cells, with definite cell-outline and a simple nucleus. These latter cells are derived from Langhans' layer (Fig. 552, p. 926 : and *cf.* Figs. 535–6, p. 910 : and Figs. 550–1, p. 925).

An important feature of such cases of chorionepithelioma is that, although these tumours act as, and in many respects are, a highly malignant type of neoplasm, yet a process of natural healing or spontaneous cure may occur in the secondary tumours, *e.g.*, in the lungs, after the removal of the primary seat of the disease.

Tumours, apparently of the nature of chorionepithelioma, also occasionally occur in the **testicle** (p. 910). These are probably teratomas, and, although syncytial and Langhans' cells are often the predominating, and sometimes the only, cells present, the majority of such tumours also contain elements representing all three germinal layers of the embryo, and, according to some writers, there may be a suggestion of the formation in them of structures bearing some resemblance to aberrant fœtal organs and tissues.

APPENDIX I

TO SECTION ON TUMOURS

SYNOPSIS OF VARIETIES OF CYSTS

1. **TRUE CYSTIC TUMOURS, CYSTADENOMAS,** or **CYSTOMAS,** arising from the proliferation of glands, mucous membranes, etc., *e.g.*, cystic tumours of the thyroid, pituitary, ovary, kidney, etc. Cysts of varying size are also common in adenomas.
2. **CYSTS ARISING FROM DEVELOPMENTAL ERRORS** :
   (*a*) **From embryonic intermingling,** *e.g.*, sebaceous and other cysts, hygromas, etc., arising at the lines of closure of embryonic clefts or in the middle line (spina-bifida, meningoceles, encephaloceles, etc.) : and the results of other accidental intermingling or inclusions.

(*b*) **Congenital Cysts,** due to the persistence and distension of fœtal structures which should normally become obliterated, *e.g.* :—

i. **Urachus.**

ii. **Remains of Wolffian** (mesonephric) **Duct** (this, in the **male,** develops into the canal of the epididymis, vas deferens, seminal vesicle, and common ejaculatory duct : in the **female,** into the longitudinal duct of the ep-oöphoron ("parovarium") and the hydatids of Morgagni (appendices vesiculosæ). In **both sexes,** it also gives rise to the ureter, pelvis, and collecting tubules of the kidney).

iii. **Remains of Müllerian** (para-mesonephric) **Ducts** (from which are normally developed the uterine (Fallopian) tubes, uterus, and vagina in the **female :** and the hydatids or appendices of the epididymis and the utriculus masculinus (prostatic utricle) in the **male**).

iv. **Remains of the Mesonephros**—part of the primitive excretory organ—from which are developed the vasa efferentia, ductuli aberrantes, and the tubules of the paradidymis (organ of Giraldès) in the **male :** and the rudimentary tubules of the ep-oöphoron and par-oöphoron in the **female.**

v. **Thyroglossal Duct,** etc.

vi. **Branchial Clefts.**

vii. **Meckel's Diverticulum** (diverticulum ilei).

(*c*) **Teratomas,** *e.g.*, " dermoid cysts."

3. **CYSTS ARISING FROM SEROUS CAVITIES,** *e.g.*, originating from, or developing in the neighbourhood of, bursæ and tendon-sheaths, may result from injury or may be proliferative. The so-called " loose-bodies " in bursæ and joints arise usually from the separation of papilliform ingrowths, which may, in some cases, undergo degeneration and become calcified. Some cysts may also arise as diverticula from serous membranes, *e.g.*, from the pericardium, pleura, and peritoneum, meninges, or from the lining of the cerebral ventricles and central canal of the spinal cord.

(The " common bunion " is a false bursa with thickened connective-tissue walls, which arises opposite the first metatarso-phalangeal joint as the result of pressure.)

4. **RETENTION-CYSTS** due to the blocking of glandular ducts or tubules by inspissated and retained secretion, calculi, etc. : for example, pancreatic cysts brought about by obstruction of the pancreatic duct or of one of its branches by calculi due to calcified mucus : " ranula," or a cystic dilatation due to the blocking of the duct of a salivary gland : cysts in the kidney due to the blocking of tubules at some part of their course by the contraction of fibrous tissue around them, or to the presence of colloid casts, etc., in their lumen.

5. **DISTENTION-CYSTS,** *e.g.*, arising from the distention of bursæ, or of the normal cystic spaces of the thyroid or pituitary gland, etc., and in certain tumours, *e.g.*, in metastases from bronchial carcinoma.

6. **SPURIOUS or FALSE CYSTS or PSEUDOCYSTS** ; for example, those due to mucinoid degeneration, or to hæmorrhages which may then become encapsulated. The latter are common in tumours, *e.g.*, in gliomas and in sarcomas, but may also follow hæmorrhage elsewhere—hæmatomas or " blood-cysts," *e.g.*, extra-dural or sub-dural, or in the substance of the brain. All hæmatomas are not necessarily spurious cysts ; for example, in the case where hæmorrhage occurs *into* a true cyst. Pseudocysts are also of common occurrence in chondromas, as the result of mucinoid degeneration.

7. **PARASITIC CYSTS** ; for example, hydatid-cysts in the liver due to the cystic stage of *Echinococcus granulosus* (*Tænia echinococcus*) : *Cysticercus cellulosæ* : coccidial cysts, common in the rabbit's liver, due to *Eimeria perforans* or *E. stiedæ.*

APPENDIX II

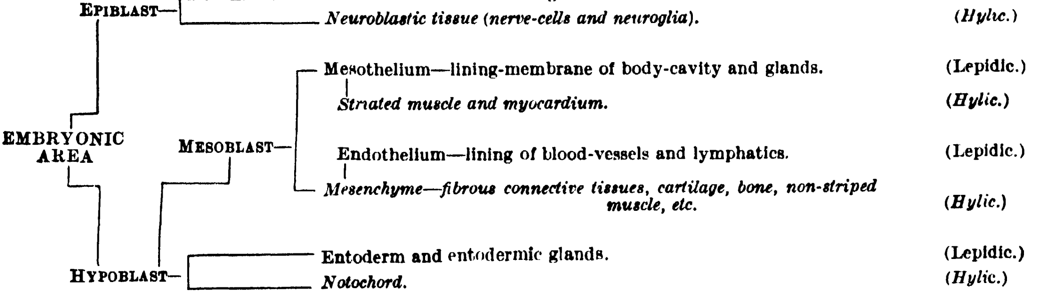
ADAMI'S CLASSIFICATION OF TUMOURS[1]

(*See* p. 297.)

It is now established that "the specific and characteristic cells of several tissues of the glandular type—of the kidneys, suprarenal bodies, ovaries, testes, and uterine mucosa —are of mesoblastic origin, but these, nevertheless, give rise to tumours which may and often do resemble most closely those of hypoblastic and epiblastic origin. . . . And thus the cancer-like tumours which originate in these organs must be accepted as mesoblastic."[1] Adami also pointed out that gliomas, though resembling sarcomas, take origin from the epiblast; whilst new growths arising from the remains of the notochord, which is hypoblastic in origin, may resemble myxomatous cartilage-like tumours. These difficulties did much to discredit attempts at an embryological classification; and Adami proceeded to show how those apparent exceptions might be reconciled with such a true embryological method.

After the differentiation of the cells of the embryo into the primitive epiblast and hypoblast (Fig. 192, p. 357), the latter gives rise, by the proliferation of its cells, to the mesoblast, but itself remains as a distinct **lining-membrane.** At the same time, the epiblast gives rise to the mass of cells which dips in and becomes detached to form the central nervous system. Similarly, the notochord is formed by a mass of cells which becomes detached from the hypoblast. Mesoblastic, neuroblastic, and notochordal tissue are, therefore, all "derived from the two primitive cell-layers, and the first two, at least, **lose the lining-membrane characteristics of these two earliest layers, and take on a less differentiated condition prior to farther evolution**" (*loc. cit.*, p. 247). Later, the mesoblast becomes farther differentiated, growing out between the epiblast and hypoblast to form or enclose the primitive body-cavity, there being now two structures of mesoblastic origin—the **mesothelium** or lining-membrane portion of the mesoblast, and the **mesenchyme** or mesoblastic pulp. From the mesothelium is derived another group of cells on either side of the embryo which becomes the "mother-tissue" of the striated muscle and myocardium; whilst the other tissues derived from the mesothelium are of the nature of lining-membranes, *e.g.*, the cells lining the pleura, pericardium, peritoneum: or go to form the special glandular cells of the suprarenal cortex, kidneys, and genital glands.

From the mesenchyme are developed the endothelial cells lining blood-vessels and lymphatics; but the bulk of tissues derived from the mesenchyme are of the nature of pulp-tissues, *e.g.*, connective tissue, cartilage, bone, etc. (*see* table).


EPIBLAST—
Ectoderm and ectodermic glands.
(Lepidic.)
Neuroblastic tissue (nerve-cells and neuroglia).
(*Hylic.*)
EMBRYONIC AREA
MESOBLAST—
Mesothelium—lining-membrane of body-cavity and glands.
(Lepidic.)
Striated muscle and myocardium.
(*Hylic.*)
Endothelium—lining of blood-vessels and lymphatics.
(Lepidic.)
Mesenchyme—fibrous connective tissues, cartilage, bone, non-striped muscle, etc.
(*Hylic.*)
HYPOBLAST—
Entoderm and entodermic glands.
(Lepidic.)
Notochord.
(*Hylic.*)

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[1] J. G. Adami: "On the Classification of Tumours," *Jour. Path. and Bact.*, 1902, 8, 243.

Thus epiblast, hypoblast and mesoblast become **each** differentiated into **two** sets of tissues :—

(1) **Lining-membrane tissues** (including the epithelial cells of glandular organs).

(2) **Pulp-tissues.**

The former, from whichever embryonic layer they originate, may either remain as functional covering- or lining-membranes, *e.g.*, the pleura, pericardium, peritoneum, skin, mucous membranes, etc. ; or they may become developed into the highly-specialised parenchymatous constituents of various glandular organs, *e.g.*, the sebaceous and sweat-glands, digestive glands, and genito-urinary glands, lining-membranes of the lungs, etc., etc. These special constituents dip down, as it were, into the mesenchyme, and thus acquire a stroma of connective tissue. They themselves, however, form layers or groups of cells into which the vessels do not penetrate, and in which there is an absence of stroma between the individual members of the cell-groups. In tissues derived from the embryonic pulp, on the other hand, **the individual cells are separated by an inter-cellular substance, either homogeneous or fibrillated.**

Adami therefore divides the various tissues of the body into two great groups :—

Lepidic (from *λεπίς*, *λεπίδος*, *lepis*, *lepidos*, a rind, skin, or membrane)—the covering- and lining-membrane group.

Hylic (from *ὕλη*, *hulē* or *hylē*, crude or undifferentiated matter)—the body-pulp group.

Explanation of Figure 192.

I. *Embryonic Area*, showing differentiation into *Epiblast* and *Hypoblast*.

II. *Embryonic Area*, showing differentiation into *Epiblast*, *Mesoblast* and *Hypoblast*. Dipping-in of Epiblast to form *Neural Canal* (N.C.).

III. *Neural Canal* (N.C.) almost complete. Differentiation of Mesoblast into *Mesenchyme* (Mes^{cm}.) and *Mesothelium* (Mesth.). Formation of *Cœlom* or *Body-Cavity* (B.C.) in the latter. Formation of *Notochord* (N.) from Hypoblast.

IV. *Neural Canal* or *Neuroblastic-tissue* (N.C.), completely separated from surface-epiblast or Ectoderm (Ect.). Formation of *Vascular Endothelium* (End^{thm}) from Mesenchyme. Differentiation of Mesothelium into *pulp-layer* and *lining-layer*. Complete separation of *Notochord* (Ncd.) from lining hypoblast or *Entoderm* (Ent.).

V. Schematic Transverse Section of Embryo, showing the derivation of the body-tissues from the three embryonic layers (modified from Adami).[1]

Primitive Layer.	*Lepidic Tissues.*	*Hylic Tissues.*
Epiblast.	Ectoderm and derived glands (Ect.).	Neuroblastic tissue (Nbl^{t}).
Mesoblast.	Mesothelium lining body-cavity (B.C.) and derived glands. Endothelium lining vessels (End^{thm}.).	Mesenchyme (Mes^{cm}.). Striated muscle formed from Mesothelium (Mesth.).
Hypoblast.	Entoderm and derived glands (Ent.).	Notochord (Ncd.).

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[1] Adami, *loc. cit.*, p. 248.

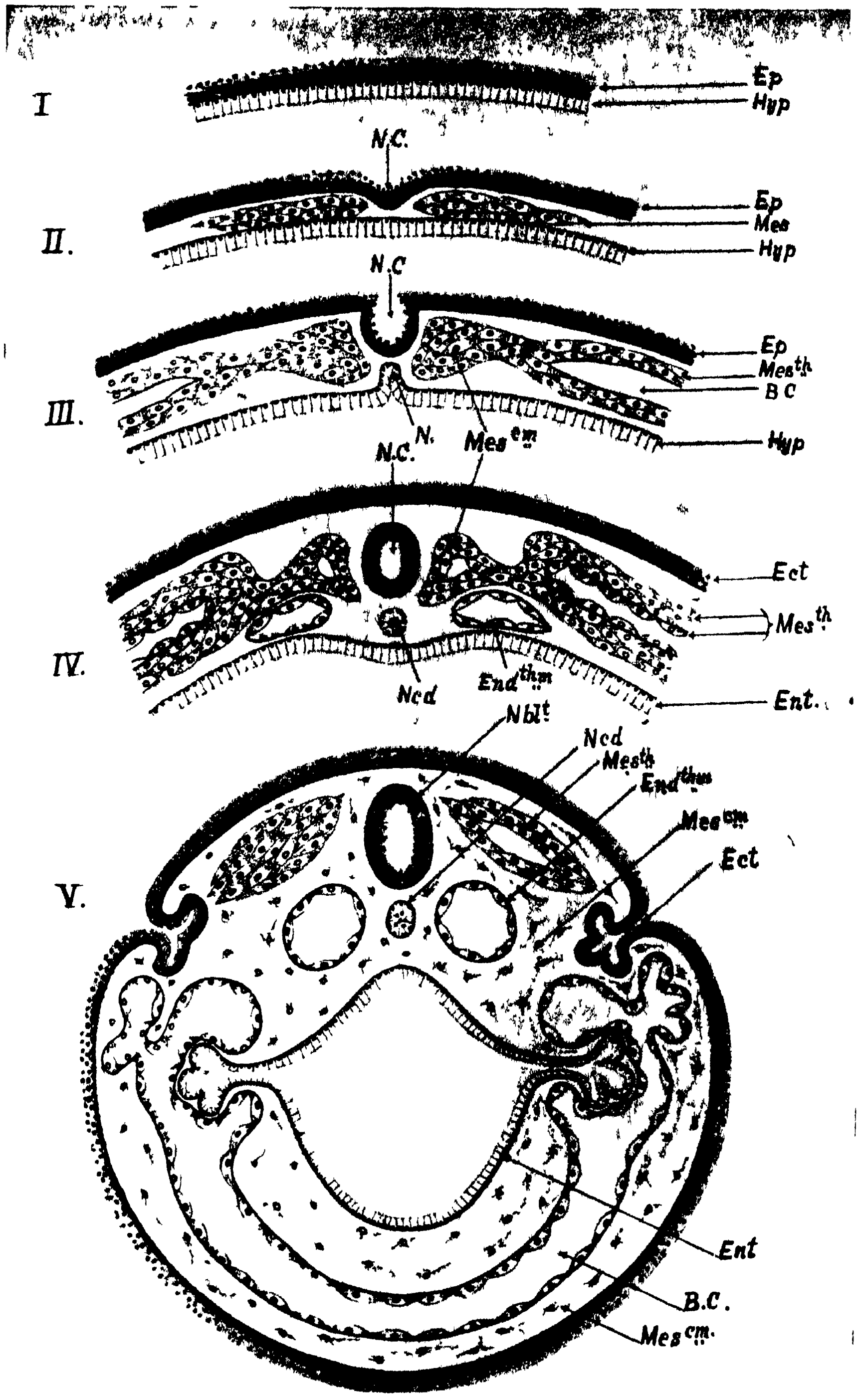

Fig. 192. *Schemes to show Embryogenetic Relationship of the various body-tissues.* (*Cf.* Figs. 129 and 130, p. 292)

The tissues in each of these main groups—**Lepidic** and **Hylic**—he further subdivides according as they are epiblastic, hypoblastic, mesothelial, mesenchymatous, or endothelial in origin; and on this basis he gives the following classification (slightly modified) of normal tissues:—

I. LEPIDIC, OR LINING-MEMBRANE TISSUES

In these, the blood-vessels do not penetrate the groups of specific cells, and there is an absence of definite stroma between the individual cells, although such stroma, of mesenchymatous origin, may be present between the groups of cells.

1. **Epiblastic.** Epidermis. Epidermal appendages—hairs, nails, enamel of teeth, etc. Epidermal glands, including breast. Epithelium of lips and mouth—salivary glands. Epithelium and glands of—nasal tract and associated spaces. Epidermal portion of hypophysis cerebri. Lens of eye. Epithelium of—conjunctiva, membranous labyrinth of ear, anus, male urethra (except prostatic portion).
2. **Hypoblastic.** Epithelium of—digestive tract and glands connected with it. Specific cells of—liver, pancreas, tonsils, thymus, thyroid. Epithelium of—trachea, lungs, bladder, female urethra, male urethra (prostatic portion).
3. **Mesothelial.** Lining-cells of—pleuræ, pericardium, peritoneum. Specific cells of—suprarenal cortex, kidneys, testes, ovaries (Graafian or ovarian follicles). Epithelium and glands of—uterine (Fallopian) tubes, uterus, vagina, vasa deferentia, vesiculæ seminales, etc.
4. **Endothelial.** Lining-endothelium of—blood-vessels, lymphatics.

II. HYLIC, OR PRIMITIVE PULP-TISSUES

Organs and tissues in which the special characteristic is that the specific cells lie in, and are separated by, a definite stroma, homogeneous or fibrillar, in which there may or may not be blood- and lymph-vessels.

1. **Epiblastic.** Nerve-cells and their processes, neuroglia (Fig. 570, p. 952).
2. **Hypoblastic.** The notochord and its remains (Fig. 139, p. 306).
3. **Mesenchymatous.** Fibrous connective tissues, cartilage, bone, reticulum of lymph-nodes, bone-marrow, fat-cells, involuntary muscle-tissue, spleen, blood-vessels, blood-corpuscles.
4. **Mesothelial.** Striated muscle, including cardiac muscle.

Adami then classifies tumours or "autonomous neoplasms" into the two great orders:—

TERATOMATA, or "tumours composed of the products of one individual within the tissues of another individual of the same species." [1]

BLASTOMATA, or "tumours composed of the products of aberrant growth of the cells and tissues of the individual in whom they are developed."

The latter, the **Blastomata,** or **Body-Tissue Tumours,** he then subdivides, according as they arise from **lepidic** or from **hylic** tissues, into two main genera, **Lepidomata** and **Hylomata,** and prefixes these, according to the embryonic layer from which they arise, as follows:—

Epi-, Hypo-, and **Meso-lepidomata.**
Epi-, Hypo-, and **Meso-hylomata.**

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[1] But, in this connection, *see under* "Experimental Embryology," pp. 291–293: and also p. 351.

THE BLASTOMATA OR BODY-TISSUE TUMOURS

I. LEPIDOMATA, OR RIND-TUMOURS:

- A. **Lepidomata of the First Order, or Primary Lepidomata** :—
  - 1. **Epilepidomata** (Lepidomata whose characteristic constituents are overgrowths of tissues derived directly from the epiblastic lining-membranes, or true epiblast).
    - (a) **Typical.** Papilloma, epidermal adenomata (of sweat, salivary, sebaceous, and mammary glands, etc.).
    - (b) **Atypical.** Epithelioma proper, carcinoma of glands of epiblastic origin. (*Re* "melanocarcinoma," *see* pp. 323–4).
  - 2. **Hypolepidomata** (Lepidomata of Hypoblastic origin):—
    - (a) **Typical.** Adenoma and papilloma of digestive and respiratory tracts, thyroid, pancreas, liver, bladder, etc.
    - (b) **Atypical.** Carcinoma developing in the same organs and regions.
- B. **Lepidomata of the Second Order, or Transitional Lepidomata** :—
  - 3. **Mesolepidomata** (Lepidomata the characteristic constituents of which are cells derived in direct descent from the persistent **mesothelium** of the embryo):—
    - (a) **Typical.** Adenoma of kidney, testicle, ovary, urogenital ducts: adenoma of uterus and prostate: "adenomas" (endotheliomas) originating from the serous membranes, "mesothelioma" of pleuræ, peritoneum, etc.
    - (b) **Atypical.** Carcinoma of the above-mentioned organs: squamous endothelioma, so-called, of serous surfaces, epithelioma of vagina, adrenal mesotheliomas, hypernephromas.
  - 4. **Endothelial Lepidomata,** originating from the endothelium of the blood- and lymph-vessels: endothelioma, perithelioma.

II. HYLOMATA, OR PULP-TUMOURS:

- 1. **Epihylomata,** or Hylomata the characteristic constituents of which are overgrowths of tissues derived from the embryonic pulp of epiblastic origin.
  - (a) **Typical.** The neuroma-glioma group (Fig. 679, p. 1098).
  - (b) **Atypical.** The glioblastoma-group ("Gliosarcoma").
- 2. **Hypohylomata,** or Hylomata derived similarly from embryonic pulp of hypoblastic origin.
  - (a) **Typical.** } Chordoma.
  - (b) **Atypical.** }
- 3. **Mesohylomata,** or Hylomata derived from mesoblastic mesenchyme and mesothelium:—
  - A. **Mesenchymal Hylomata.** Derived from tissues originating from the persistent mesoblastic pulp or mesenchyme.
    - (a) **Typical.** Fibroma, lipoma, chondroma, osteoma, myxoma, leiomyoma, myeloma.
    - (b) **Atypical.** Sarcoma (derived from mesenchymatous tissues), with its various subdivisions, fibro-sarcoma, spindle-celled sarcoma, chondrosarcoma, osteo-sarcoma, myxo-sarcoma, etc.: (of origin still debated, melanoma—see pp. 323–4).
  - B. **Mesothelial Hylomata,** or Hylomata which are overgrowths similarly of tissues derived from embryonic pulp of definitely mesothelial origin.
    - (a) **Typical.** } Rhabdomyoma.
    - (b) **Atypical.** }

CHAPTER XIV

ANIMAL PARASITES[1]

Parasites may be defined as organisms which live, either temporarily or permanently, in the tissues or organs, or upon the surface of other organisms, from which they obtain shelter and derive, partially or entirely, their nutriment. Such parasites may belong to the vegetable kingdom, the **Phytoparasites,** *e.g.*, bacteria and moulds : or to the animal kingdom ; and it is to the latter—the **Zoöparasites**— that reference will be made in this chapter. The most important " permanent " animal parasites which infest man belong either to the **Protozoa** or to the **Helminthes, Vermes** or **Worms,** a somewhat heterogeneous group of the **Invertebrate Metazoa**— classified biologically from their habits, rather than systematically. Less important *as parasites*, and for the most part occasional, temporary or incidental, but sometimes of great importance *as carriers of disease*, are certain members of the **Insecta** and **Arachnida** (*spiders, mites, ticks*, etc.) groups of the **Arthropoda.**

All degrees of parasitism are found, the permanent parasites being mainly **entozoa** or **endoparasites** (*i.e.*, living within the body of their **host,** as the animal which harbours the parasites is called) ; the occasional parasites being for the most part—though not invariably—**epizoa** or **ectoparasites,** *i.e.*, surface parasites, such as fleas, lice, bugs, ticks, etc. Some ectoparasites, such as mosquitoes and other biting flies, leeches, etc., seek their host merely for the purpose of obtaining a meal. Others, *e.g.*, lice, may live upon the body of their host throughout their entire life-cycle.

For the completion of their life-cycle, the great majority of animal parasites, more particularly the entozoa—both proto- and meta-zoön—require to pass their **mature** and their **immature stages** in different hosts often widely separated in the zoölogical scale : the **final** or **definitive host** harbouring the mature, and the **intermediate** or **temporary host** harbouring the immature, forms of the parasite. Only in rare instances among the helminthes, *e.g.*, in *Trichinella,* does the whole cycle of development occur within the body of the same host. In many cases, a specific variety of host is required before the development of the parasite can occur. The special site in the body of the host occupied by the parasite is known as the **habitat.**

From the fact that parasites, more especially the entozoa, obtain shelter and nourishment from their hosts, their bodies are usually much modified as compared with those of their free-living relatives in the zoölogical scale. In many instances, such parasites pass some stage of their life-cycle as free-living organisms, and then, on entering their host, undergo striking structural changes adapted to a parasitic mode of life—the more or less passive absorption of nourishment and the reproduction of their species, the latter function being developed usually to an excessive degree, in order to compensate for the vicissitudes and dangers of such an existence, more especially the chances of not obtaining a suitable new host. Organs connected with free-living functions usually retrogress and may be lost; for example, eyes and other sense-organs, the digestive system, organs of locomotion, etc., may remain rudimentary or may completely disappear. On the other hand, special organs may be developed to facilitate their entrance into, and their stay in, the body of their host, for example, biting and boring apparatus, hooklets, suckers, etc. Such modifications of structure and function may take place in the life-history of the race, or during the life-cycle of each individual parasite; or, in some instances, they may occur only in certain generations of parasites which show the phenomenon known as alternation of generations.

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[1] For fuller descriptions of the various animal parasites described in this chapter, and for an account of those which have been omitted on account of their rarity, reference should be made to : " Précis de Parasitologie," by E. Brumpt, 5th ed. (1936), Masson et Cie., Paris ; " Protozoology." by J. G. Thomson and A. Robertson (1929), Baillière, Tindall & Cox, London ; " The Intestinal Protozoa of Man," by Dobell and O'Connor (1921), John Bale, Sons & Danielsson, London ; " Tropical Medicine," by Leonard Rogers and J. W. D. Megaw, 4th ed. (1942), Churchill, London ; " Tropical Diseases," by Manson-Bahr, 11th ed. (1941), Cassell, London ; " Human Intestinal Protozoa in the Near East," by Wenyon and O'Connor (1917), Wellcome Bureau of Scientific Research, London,

Parasites may be **specific** to certain hosts, *i.e.*, found in them only; or incidental, *i.e.*, occurring only occasionally in a species other than the usual host.

Effects of Parasites upon their Hosts. These may vary from a trifling and temporary inconvenience, such as the bites of certain insects, up to the most serious or fatal diseases, *e.g.*, malaria, sleeping sickness, yellow fever, trench-fever and bacterial diseases such as plague, tetanus, or septicæmia. Similarly, certain intestinal parasites may produce but little or no apparent symptomatic results in one case, and serious disease in another, *e.g.*, in the "carrier" of the entamœba of dysentery, and in the patient suffering from the disease itself in severe form, respectively. Certain tapeworms and other parasitic worms may do little harm in one host; whilst serious phenomena, *e.g.*, grave anæmia, may result from their presence in another. Important organs may be extensively damaged (*e.g.*, the bowel or liver in amœbic dysentery), or compressed and injured, as in hydatid-cyst infestations.

The methods and routes by which parasites invade their hosts and reach their habitat in the host's body are described most conveniently when dealing with the individual parasites.

As the subject of parasitology is now very extensive, and numerous special books dealing with it have appeared, we refer our readers to these for an account of any parasites not dealt with in the following pages.

NOTE.—The term "Pseudo-parasite"—an unfortunate word which it is best to avoid—is often applied to certain structures, *e.g.*, vegetable-fibres, etc., which may simulate and be mistaken for parasites, for example, certain fibres of banana which, when partially digested, have, in the fæces, a superficial resemblance to small worms; whilst certain seeds and other vegetable cells may simulate the ova of parasitic worms. One may also note, in this connection, that normal or degenerated cells of the host have sometimes been mistaken for parasites, *e.g.*, desquamated intestinal and other epithelial cells for amœbæ: or spermatozoa (especially of birds) for trypanosomes.

REACTIONS OF THE HOST TO PARASITES. Local. An inflammatory reaction occurs, as against any other foreign body, and this may destroy the invading parasite. In some cases, the reaction is of the nature of a granulomatous formation, as in the rectum affected with *Schistosoma* (*Bilharzia*), where there may be formed polypoid masses of tissue. The parasite may become encapsulated and so prevented from doing further harm, *e.g.*, *Trichinella* in muscle. Or again, especially around worms or their eggs, there may be a local infiltration of eosinophil leucocytes, a reaction which, however, is not necessarily peculiar to parasitic infestation. Grave symptoms of disease on the part of the host in some instances tend to supervene more particularly on the death and degeneration of the parasite, as in cysticercosis of the brain (pp. 397 and 1153).

General Reactions. In the Blood. In many cases, there is a definite and characteristic reaction on the part of the leucocytes. In malaria and leishmaniasis, the large mononuclears are relatively increased, and may show ingested pigment. In infestation with parasitic worms, there is frequently an eosinophilia both relative and absolute. The parasite itself may be demonstrable in the blood, as in malaria and spirochætosis. Antibodies to parasites may be formed, *e.g.*, precipitins in the case of hydatid-disease, agglutinins in trypanosomiasis, etc. Serological diagnosis is thus possible in such cases.

In other Organs. Frequently, the spleen is greatly enlarged, for example in malaria and kala-azar. Lymph-nodes may be enlarged and harbour the parasites in trypanosomiasis. The liver and bone-marrow are frequent sites of the accumulation of parasites, and diagnosis may sometimes be facilitated by the examination of biopsy-specimens obtained by sternal puncture (p. 606); whilst a few varieties may occur and be demonstrable in the cerebrospinal fluid (p. 1156). The fæces and urine may contain either the adult parasites, *e.g.*, certain tæniæ, or the ova, *e.g.*, of *Schistosoma*. The sputum may show ova of the lung-trematode, *Paragonimus ringeri* (p. 385).

SECTION I

PROTOZOA

Classification of Parasites. As there are difficulties and irregularities in the classification of parasites, we think it sufficient to deal with them, in relation to their association with disease, under the two great divisions of **Protozoa** and **Metazoa.** Where desirable, reference will be made to the special Class or Order to which any parasite belongs.

PARASITES OF THE CLASS AMŒBÆ

1. **ENTAMŒBA HISTOLYTICA.** (Syn. *E. dysenteriæ*, *E. tetragena*, etc.). This parasite, which is the cause of true tropical or amœbic dysentery—as distinct from bacillary dysentery—is an inhabitant primarily of the large intestine (pp. 748 and 778).

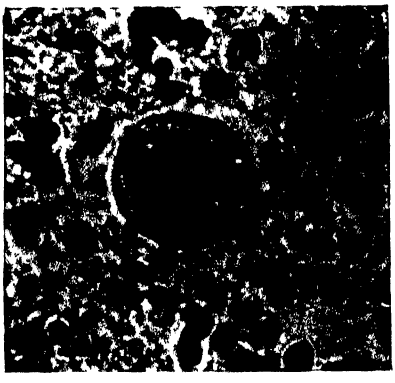

FIG. 193. *Entamœba histolytica* in an abscess of the liver. × 1000.

Characters of *Entamœba histolytica.* In its amœboid or vegetative phase, it consists of an irregular mass of protoplasm, 18 to 40 μ—usually 20 to 30 μ—in diameter, which is definitely divided into a clear hyaline ectoplasm and a granular endoplasm. When at rest or dead, the entamœba is spherical, but, when examined on the warm stage whilst still alive and fresh, it may show active movement, flowing along with a rapid slug-like motion, or, when slightly degenerated, remaining in one place and showing the characteristic sudden projection of blunt rounded knob-like pseudopodia (Fig. 194, *a* and *c*). When first protruded, these pseudopodia consist of clear colourless transparent

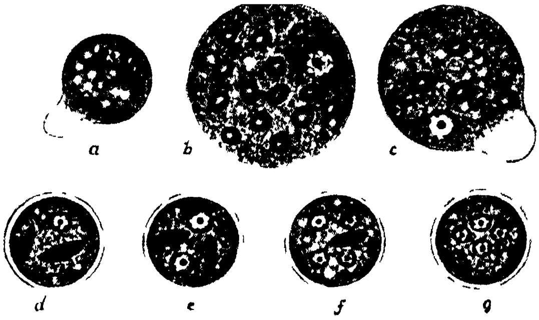

FIG. 194. *Entamœba histolytica.*

a. Small active tissue-invading amœba, with characteristic knob-like ectoplasmic pseudopodium.
b. Large active tissue-invading amœba containing numerous ingested red blood-corpuscles in cytoplasm.
c. Ditto, showing pseudopodium.
d, e, f, g. Encysted forms with one, two, and four nuclei—hence the name *E. tetragena.* Chromatoid bodies are seen in the first three of these. × 1000.

ectoplasm only, into which the more granular endoplasm then flows. The nucleus is small and often placed at one side of the body. It is poor in chromatin and hence difficult to stain well. The endoplasm usually shows numerous bubble-like vacuoles, giving a foamy or froth-like appearance. Digestive vacuoles may be present and contain various inclusions, especially red blood-corpuscles, leucocytes, and fragments of other cells—bacteria being exceptional as inclusions. A true contractile vacuole is absent. Blunt chromatoid bodies or rods (so named because they give some of the reactions of chromatin) are usually demonstrable. In the acuter stages of the disease, active amœbæ of larger size are usually found, these being the tissue-invading and tissue-inhabiting phase of the parasite. The smaller forms which replace them in the convalescent and carrier stages of the disease precede the formation of cysts. In its active or vegetative condition in the tissues, the parasite multiplies by binary fission, the nucleus dividing by a process described by Dobell as appearing to belong to a category intermediate between amitotic and mitotic division.

Sizes and Species of Entamœbæ. Whilst the size given—20 μ to 30 μ—is that usual for the entamœba, smaller forms also occur and have been named "*minuta*." The encysted forms of these tend also to be smaller. Dobell has suggested the recognition of several species of *Entamœba histolytica* based on their size. Brumpt has emphasised that, whilst there may be small varieties of *E. histolytica*, there are other entamœbæ which so closely resemble *E. histolytica* that they have been confused with it. Of these, two are of importance from this point of view—*E. dispar* and *E. hartmanni*. Both are small, both have small cystic forms containing four nuclei. They are widely distributed geographically and may be found in fæces of many individuals. In the published tables (*see* Brumpt) of the incidence of *E. histolytica* in stools, there is quite an appreciable percentage given for countries where amœbic dysentery is practically unknown. According to Brumpt, this is due to confusion between *E. histolytica* and those forms closely resembling it morphologically. *E. dispar* is very slightly pathogenic to the cat, and *E. hartmanni* is non-pathogenic to that animal. *E. histolytica*, on the other hand, is definitely pathogenic to the cat, producing dysenteric ulceration and even liver-abscess.

Neither *E. dispar* nor *E. hartmanni* ingest red blood-corpuscles, and thus differ in this respect from *E. histolytica*.

Encystment. Probably at any period of the infestation, but especially when the conditions are unfavourable for vegetative activity, for example during the process of healing of the dysenteric ulcers or abscesses, or if the fæces become hard and constipated, the active amœboid organism undergoes a series of simple divisions, extrudes any englobed food-particles, and becomes reduced in size. These amœbæ are intermediate in size, forming a series between the larger tissue-inhabiting forms and the smaller cysts to which they give rise. They are sluggish and finally non-motile ; become spherical in shape, and develop a definite wall. The cytoplasm becomes finely granular, the distinction between ecto- and endo-plasm being lost, division of the nucleus occurs, giving rise first to two, then to **four,** nuclei lying in pairs within the cyst. Any glycogen and chromatoid bodies that have remained gradually disappear. The quadrinucleate cysts are now mature and ready to be ingested by a new host.

The size of these cysts varies considerably in different cases, a range of 5 to 20 μ for the diameter being given by various authors. The cysts are fairly resistant, and may survive for several weeks outside the body, if kept moist and cool. They are quickly killed by drying, and degenerate more rapidly at high than at low temperatures. In the chlorination of water, for the purpose of destroying infecting bacteria, the entamœbæ are not readily killed.

The cyst-wall is little affected by gastric digestion, but is rapidly dissolved by trypsin. Schaudinn, by feeding kittens with dried fæces containing cysts, succeeded in producing dysentery in these animals, great numbers of amœbæ being found in their intestines ; and similar experiments have been successful in the human subject—the incubation-period varying greatly, but averaging about nine days until the appearance of cysts in the stools, and just over two months till the development of dysenteric symptoms in the few cases which developed these. Such experimental observations support the view that *E. histolytica* is a cause of dysentery ; but stronger evidence is the regularity with which the organism is found in this disease, and the constancy of its relationship to the primary and secondary lesions. All strains of *E. histolytica* are capable of producing either carrier- or active dysentery-infestations, and Dobell believes that " virulent " and " non-virulent " races of the parasite do not occur, the clinical differences being explained rather in terms of the varying susceptibility or resistance of the hosts. The infestation is conveyed from man to man by the contamination of food or drink with fæcal matter containing the cysts. Flies act as agents in this contamination and viable cysts have been found in their dejecta. *E. histolytica* has been cultivated in suitable artificial media by A. C. Boeck and J. Drbohlav in America (1925) : and J. G. Thomson and A. Robertson (1925), C. Dobell and P. P. Laidlaw (1926), and others in this country.

Amœbic Infestation. The parasite in its cystic form is ingested in contaminated food. It passes unharmed through the stomach and " excysts," or matures, assuming the amœboid form in the intestine. It becomes established in the cæcum and colon and invades the mucosa, working its way into the submucosa where it causes necrosis of tissue, undermining the superficial layers of mucous membrane ; these layers eventually give way and so the amœbic ulcer is formed, which may increase in size and cause much destruction of tissue with extensive ulceration. Hæmorrhage from eroded vessels occurs and there is an excessive production of mucus from irritation of the mucous glands. The disease may become chronic, with fibrosis of the wall of the intestine (pp. 748–50) In the stools, the amœbæ are found especially in the material showing blood or mucus. In the lesions of the bowel, the amœbæ lie especially in the advancing edge and can be seen entering small blood-vessels. In this way they may reach the liver and there set up liver-abscess (p. 778 and Fig. 436, p. 779). Whilst intestinal ulceration is the usual lesion, this is followed in a considerable percentage of cases, by liver-abscess ; and, whilst cutaneous amœbiasis in the neighbourhood of the anus is fairly frequent, lesions elsewhere in the body are distinctly rare—amœbic brain-abscess has been found in a few cases.

The Carrier-State. Carriers of *E. histolytica* may be (*a*) persons who have shown clinical evidence of amœbic dysentery and who have recovered, or who suffer from occasional recurrences of symptoms, or (*b*) those who have never exhibited any definite clinical signs of the disease. The latter may have had the infestation without symptoms. It has been demonstrated by various observers, and we can confirm this from personal experience, that there may be found, on post-mortem examination, amœbic ulceration of the intestine, or healed scars of ulcers in persons who have never shown any active clinical symptoms of dysentery.

In the carrier, cysts may persist in the fæces for many years; and an acute attack or a recurrence of the active disease may supervene long after the primary infestation—as much as thirty years in one case known to us.

OTHER ENTAMŒBÆ. These are of interest because of the possibility of their being confused with *E. histolytica.* They are non-pathogenic. For details of their morphology, etc., see the references given.

2. **ENTAMŒBA COLI** (Syn. *Amœba coli, Entamœba hominis,* etc.).—This parasite lives chiefly in the cæcum and "upper" (proximal) part of the large intestine, and is a harmless commensal of its host. It is the commonest protozoön found in the human intestine, and it is especially frequent in convalescents from dysentery and other intestinal disorders, and by no means infrequent in apparently healthy persons. It has frequently been mistaken for *E. histolytica,* and *vice versâ.* Its amœboid form consists of an irregular mass of protoplasm with a large rounded, or slightly ovoid, nucleus which is rich in chromatin, aggregated especially in coarse granules attached to the nuclear membrane. No definite distinction can be made out between ectoplasm and endoplasm except during the formation of pseudopodia, when the ectoplasm appears as a clear, homogeneous, comparatively non-refractile substance into which granules from the endoplasm flow—the movements being usually comparatively sluggish. It often has a somewhat greenish tint, owing probably to the refractile character of its contained granules, whereas *E. histolytica* appears colourless. *E. coli* feeds on bacteria, yeasts, and various substances contained in the intestine, and it may even ingest other protozoa, encysted and non-encysted; but it does *not* englobe red blood-corpuscles or tissue-elements, as does *E. histolytica*—a fact of diagnostic value; and also, unlike the latter, it does not penetrate the mucous membrane. Its endoplasm shows numerous food-vacuoles, but possesses no contractile vacuole.

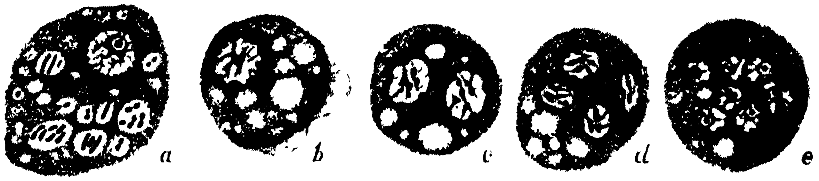

FIG. 195. *Entamœba coli.*

a. Active amœba in human fæces, showing the structure of "resting" or "vegetative" nucleus, and ingested bacteria in digestive vacuoles in cytoplasm.
b. Pre-cystic amœba, showing structure of nucleus and vacolated cytoplasm. Note absence of ingested bodies. Two pseudopodial projections are depicted.
c. Binucleate cyst with glycogen "vacuoles" in cytoplasm.
d. Quadrinucleate cyst with small chromatoid bodies in cytoplasm.
e. Mature cyst, showing eight nuclei in "resting" condition (compare with the nuclei in (*c*) and (*d*), which are in an active state of division), and chromatoid bodies in cytoplasm. The glycogen "vacuoles" have almost disappeared. × 1000.

In the intestine, particularly the proximal or "upper" part of the colon, and especially in soft fæces, multiplication takes place by simple binary fission. In the more solid and formed fæces in the lower part of the large intestine, encystment occurs and the cysts are discharged in the stools. In this process of encystment, the amœbæ extrude their food-inclusions, and become reduced in size, probably by a process of division into smaller pre-cystic forms, as in the case of *E. histolytica.* The pre-cystic stages of these two parasites are frequently very difficult to differentiate from one another. The pre-cystic amœbæ become spherical, and develop a transparent protective envelope. In this encysted cell, the nucleus first divides into two, then into four, and, finally, into the characteristic **eight,** daughter-nuclei, of equal size, protected within the thick cyst-wall. Glycogen is usually abundant in the earlier stages of this process, especially in the bi-nucleate cysts ; but it is absent, as a rule, in the 8-nucleate stage. Chromatoid bodies are not always present, and are usually scanty and small in size and acicular or filament-like, and only occasionally as abundant as in *E. histolytica.* Before further development can take place, the encysted cell requires to be taken into the intestine of a new host, the cyst-wall disintegrates, and the eight small amœbæ are set free.

E. coli cysts measure usually about 15 to 20 μ in diameter, though smaller and larger forms are sometimes found (10 to 30 μ or even more).

3. **ENTAMŒBA GINGIVALIS** (Syn. *E. buccalis, Amœba dentalis,* etc.). This parasite has been described as occurring in the mouths, especially the gums, of sufferers from dental caries and pyorrhœa ; though it may also be found when these conditions are not in evidence. Its presence appears to be of little or no pathogenic significance, and, like *E. coli,* it seems to be merely a harmless commensal. It somewhat resembles *E. histolytica* and *E. coli* in its various morphological characters.

4. **ENDOLIMAX NANA** (Syn. *Entamœba* or *Amœba nana,* etc.). This parasite is a small amœba, measuring 5 or 6 to 10 or 12 μ in diameter, the average size being about 8 μ. It is described by Wenyon and O'Connor[1] as one of the commonest protozoa in the human intestine in Egypt.

5. **IODAMŒBA BÜTSCHLII** was first recorded by Prowazek in 1912. Its cysts have been described by Wenyon under the name of "Iodine-cysts," "I-cysts," or "I-bodies," because of the presence of a peculiar iodine-staining glycogen-mass in the spherical, ovoid or irregularly-shaped cysts. The amœboid form is a small organism, intermediate in size between *E. coli* and *E. nana,* for both of which it may be readily mistaken.

6. **DIENTAMŒBA FRAGILIS** is a small amœba, averaging some 8 to 9 μ in diameter. The living amœboid form is very actively motile. The majority possess two nuclei, which require to be stained to render them clearly visible.

7. **E. DISPAR,** and (8). **E. HARTMANNI** are mentioned on p. 364.

FLAGELLATE PARASITES

1. **TRYPANOSOMA.** There are many species of these organisms, some of which are specific for their particular host, whilst others can be transmitted to hosts of differing species. Some of the trypanosomes parasitic in mammals are of importance because of their pathological effects ; others seem to live and multiply in their hosts without producing any obvious disturbance. Among the former are *T. brucei* of **nagana,** a disease of horses, cattle, and other mammals in certain parts of Africa : *T. evansi* of **surra,** occurring in horses and cattle in India and elsewhere : *T. equinum* of **mal de caderas** in horses in South America : *T. equiperdum* of **dourine** (stallion's disease) in horses in Algeria and other countries : the rat-trypanosome, *T. lewisi* : and the especially important *T. gambiense,* the organism of **sleeping**

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[1] *Loc. cit.,* p. 90.

sickness and **Gambia fever** in the human subject, and *T. rhodesiense*, which closely resembles it. The latter is more virulent to laboratory- and certain other animals, and various serological differences between the two have been described. In South America is found *T. cruzi*, which causes disease in man.

All these species present morphological features which are practically identical, and which render distinctions on morphological grounds alone almost impossible. There is considerable polymorphism in the various species, and by various manipulations it is possible to transform one so that it becomes morphologically indistinguishable from another ; indeed, it is not improbable that *T. gambiense*, *T. rhodesiense*, *T. evansi* and others may be variants of *T. brucei*. They all possess an eel-like body, along one side of which runs a fin-like protoplasmic structure, the undulating membrane. In stained films, the principal or trophic nucleus is clearly seen near the centre of the body. At or near the posterior extremity of the body is a granule or rod of chromatin, the blepharoplast or kinetic nucleus (micronucleus or centrosome). The flagellum takes origin at or near this blepharoplast, and passes along the free edge of the undulating membrane, following all its sinuosities, and reaching to the anterior extremity of the body, where it may either terminate or be prolonged for a variable distance as a free flagellum. The parasite is actively motile. Multiplication in the blood takes place by longitudinal binary fission. The blepharoplast and the nucleus divide first, and this is followed by the division of the flagellum and the body of the organism. In some trypansomes, *e.g.*, *T. lewisi*, repeated binary fission may occur, the daughter-forms remaining attached to one another by their posterior ends, leading to the formation of bunches or rosettes of the parasites. Resting or non-flagellate forms, usually small ovoid bodies, can be found in the bone-marrow, spleen, and other internal organs of the vertebrate host.

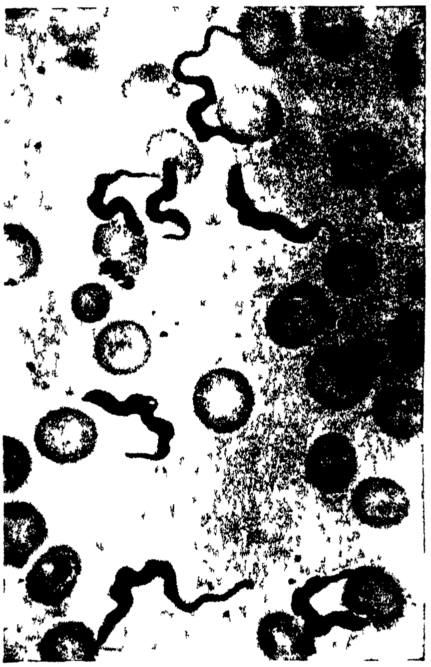

FIG. 196. *T. gambiense* in the blood of a case of sleeping sickness. × 1000.

Transmission takes place by the direct inoculation of the adult forms. In sleeping sickness, the tsetse-fly, *Glossina palpalis*, having sucked infested blood from one person, may infect another if it bites within forty-eight hours.

Usually, however, a further phase of the developmental cycle occurs in the fly, that is to say, for full development, a second invertebrate host is probably necessary. A possible exception to this general rule is the case of *T. equiperdum* of dourine, where transmission is said to take place by coitus. For the others mentioned, a dipterous insect is the second host required, *T. gambiense* being transmitted by *Glossina palpalis*, and *T. brucei* by a tsetse-fly, *Glossina morsitans*, which is also the probable insect-carrier of *T. rhodesiense*. *T. lewisi*, the rat-trypanosome, is carried from rat to rat by the rat-flea, and probably also by the dog-flea. In the case of aquatic animals, the trypanosomes are transmitted probably by leeches. In the blood of infected mammals, the parasites may be pleomorphic, for example, in the case of *T. gambiense*, long thin, and short stumpy, forms may be found, and the presence of intermediate forms suggests that these morphological variations are merely phases of division and growth.

Trypanosomes have been cultivated in artificial media by Novy and McNeal, J. G. Thomson, Sinton, and others. The specificity of the mammalian and insect-hosts required, and various immunological phenomena, *e.g.*, "trypanolysis," (analogous to bacteriolysis), serum-treatment, etc., have been investigated, and are of importance in connection with the differentiation of the trypanosomes.

Development in the Insect-Carrier, *e.g.*, **in the Tsetse-Fly** (*Glossina*). The trypanosomes (*e.g.*, *T. gambiense*), ingested with the infested blood, undergo multiplication in the mid-gut of the insect. After ten or twelve days, long thin forms appear, which migrate forwards into the proventriculus, from which they then pass to the hypopharynx and along the salivary ducts, to reach the salivary glands some sixteen to thirty days after the fly's feed. In the salivary glands, the long slender trypanosome-forms develop into shorter and broader so-called crithidial forms. These multiply in the glands and then differentiate again into short, broad trypanosome-forms, which are infective when the fly again bites the mammalian host.

For further details of the life-histories of other varieties of trypanosomes, the reader is referred to "Précis de Parasitologie," by Brumpt (*see* footnote, p. 360).

SLEEPING SICKNESS (African Trypanosomiasis). This is the disease produced in man by the trypanosomes *T. gambiense* and *T. rhodesiense*. It must not be confused with so-called "sleepy sickness" or "encephalitis lethargica" (epidemic encephalitis), due to a filtrable virus (p. 109).

Following the bite by an infested tsetse-fly (*Glossina palpalis* or *G. morsitans*), the adult trypanosome enters the blood-stream. After a variable period of incubation (ten to fifteen or more days), during which the parasites are multiplying and invading the body, there is irregular fever, insomnia and lassitude and the lymph-nodes swell. Death may occur in this acute stage, but more frequently the illness continues, with much cutaneous hyperæsthesia. Gradually, mental deterioration, drowsiness and coma supervene and death results from asthenia, or from some intercurrent infection.

The pathological changes produced are due probably to toxic substances formed by the trypanosomes. There is anæmia. The lymph-nodes are congested, sometimes hæmorrhagic, and, later, show degenerative and fibrotic changes. The spleen is congested and there is endothelial proliferation. The brain shows perivascular lymphoid collections and, later, gliosis with atrophy of nerve-cells; the meninges may be thickened and infiltrated with lymphocytes. The other organs show no characteristic changes. Trypanosomes are usually present in the blood, though often scanty: in the enlarged lymph-nodes in the early stages: and in the cerebrospinal fluid (p. 1156). Antibodies are formed and may be detectable in the blood.

The geographical distribution of the disease follows the distribution of the insect-vectors. It is endemic in large areas of Central Africa, as indicated by the names of the parasites—*T. gambiense* and *T. rhodesiense.* It has been *reported in the Sudan by Archibald.*

T. CRUZI. *This parasite is found over large areas of South America (Argentine, Brazil) and differs from the preceding forms in minor details of its morphology. The agent of infestation is a large bug—Triatoma megista (syn. Conorhinus megistus—p. 436).* The biological interest of this trypanosome is that, having entered the blood, it rapidly spreads throughout the body and settles in cells, especially in muscle-fibres, wherein it undergoes a cyclical series of changes by division, giving rise to "crithidial" forms and forms resembling Leishman-Donovan bodies (see below). Forms undergoing division are not encountered in the circulating blood. Infestation with *T. cruzi* is known as **Chagas' disease,** after the Chagas who first described it and studied the parasite. In children it is often rapidly fatal, whilst in adults a chronic form is commoner. There is fever, œdema and thyroid enlargement, progressing to myxœdema in chronic cases (p. 836). There may be also nervous changes somewhat resembling those of the African trypanosomiasis (p. 369).

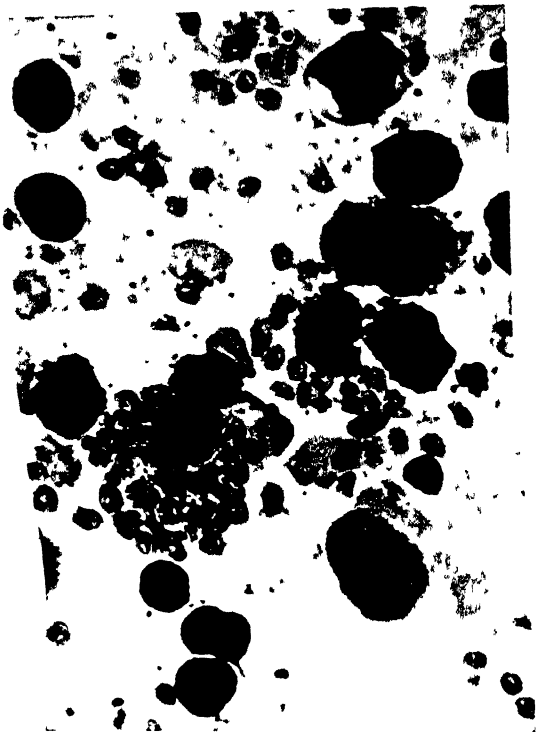

FIG. 197. Leishman-Donovan bodies from the of a case of kala-azar. × 1000.

2. **LEISHMANIA.** This Genus includes three Species :—

(i) **Leishmania donovani,** the parasite of "**Indian**" **Kala-Azar (Leishmaniasis),** a disease which occurs also in Ceylon, Burma, Indo-China, China, Syria and the Sudan, and is characterised by progressive emaciation, enlargement of the spleen and anæmia with leucopenia. The "Leishman-Donovan bodies," as they are usually called, after Leishman and Donovan, who almost simultaneously discovered them (1903), are the resting phase of a flagellate. They are minute, rounded, ovoid or slightly pear-shaped bodies, measuring 2 to 4 μ by 1·5 to 2 μ, and having a distinct cuticle. The cytoplasm contains two masses of chromatin—a larger spherical "nucleus," placed at one pole of the short axis of the body, and a smaller rod-shaped "micronucleus" (the kinetic nucleus, centrosome or blepharoplast), placed at the opposite pole. These parasites are mainly intracellullar, and are found in enormous numbers in the reticulo-endothelial cells of the spleen, liver, lymph-nodes, intestinal mucous membrane and bone-marrow. They may also occur in comparatively small numbers in the circulating blood, being taken up mainly by the large monocytes.

The insect-vector is the *Phlebotomus,* various species of this sandfly being incriminated. The parasites are found in the pharynx of this insect and are injected into the human subject by biting. In the sandfly and in culture (Rogers), "leptomonal" forms are found. These are elongated organisms with a terminal flagellum and resemble the stages of the trypanosome seen in the *Glossina* and in culture.

(ii) **Leishmania tropica,** the parasite of **Cutaneous** or **Dermal Leishmaniasis** (sometimes known as **Oriental** or **Tropical Sore, Delhi-Boil, Aleppo-Button**—though a similar lesion occurs also in South America and elsewhere), is very similar morphologically to *L. donovani*. This disease affects the exposed skin-surfaces of the human subject, and also of the dog and other animals.

(iii) **Leishmania infantum,** the cause of **Infantile Kala-Azar,** around the Mediterranean littoral, in Russia, and elsewhere, so closely resembles *L. donovani* that by some the two organisms are believed to be identical, though minor differences are described. Dogs, kittens, and, occasionally, human adults, as well as infants, are affected naturally, whilst monkeys are easily inoculable. The parasite is carried by sandflies. If the host recovers, a lasting immunity is conferred by one attack of the disease.

In all the **Leishmania** affections, the parasite attracts especially the large mononuclear phagocytes. These cells, which may be stuffed with numbers of *Leishmania*, accumulate in masses in the skin, mucous membranes, and in the spleen and lymph-nodes. They thus account for the nodules seen in the disease and for the enormously enlarged spleen seen in the kala-azar form of it.

INTESTINAL FLAGELLATES. There are numerous protozoa of this class found as inhabitants of the intestines. Among the commonest are *Trichomonas hominis* (syn. *T. intestinalis, Cercomonas intestinalis*) : *Chilomastix mesnili* (syn. *Tetramitus mesnili, Macrostoma mesnili*) : and *Giardia intestinalis.* Most of these are apparently non-pathogenic, but some, *e.g.*, *Giardia,* are associated with, if not the cause of, intestinal catarrh and diarrhœa.

Though most are found in the large intestine, the usual habitat of *Giardia* is the small bowel ; and *Trichomonas* has been noted in the mouth and in the vagina, as well as in the intestines.

GIARDIA. The only important member of this genus is **G. intestinalis** (syn. *Lamblia intestinalis, Megastoma entericum*) which is a comparatively common intestinal parasite in man, and, though regarded by many as non-pathogenic, is sometimes a cause of chronic intestinal irritation and catarrh. It frequently occurs in patients suffering from other infections and diseases of the gastro-intestinal tract, such as dysentery, intestinal cancer, etc. *Giardia* inhabits especially the duodenum and jejunum, to the mucous membrane of which it adheres by means of a large oblique sucker-like depression, with a raised margin, on the anterior portion of the ventral aspect— the dorsum being convex, and the posterior tapering extremity or tail terminating in two flagella. Three other pairs of flagella (the positions of which can be seen in Fig. 198, p. 372) originate in a paired, centrally placed, rod-like organ, the axostyle, on each side of which, laterally, is a nucleus, giving a peculiar face-like appearance to the organism. If examined in recently passed specimens of fæces, this unencysted form of the parasite is seen to be actively motile, but it soon loses its motility. It may make its way into the intestinal tubular mucous glands. It varies in length from about 12 μ to 18 μ. Individuals infested with *Giardia* often pass the encysted form in the fæces in enormous numbers, the free form being found usually only during attacks of diarrhœa. The cysts are ovoid or slightly egg-shaped bodies (10 to 15 μ long, and 7 to 9 μ across), within which may be seen either two nuclei, or two pairs formed by the division of these and the paired rod-like organ. Within these cysts, division into two usually takes place, the resulting pair of embryos lying closely packed "heads and tails,"

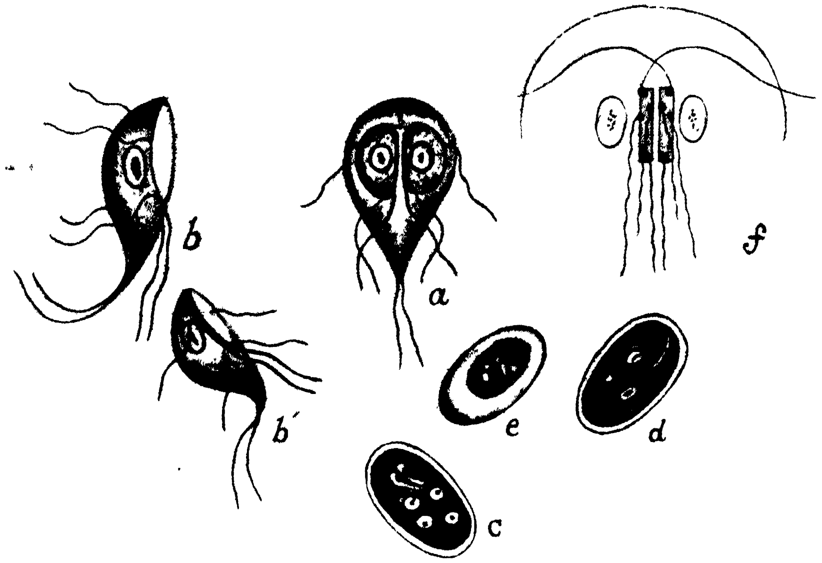

FIG. 198. *Giardia intestinalis.*

a. Ventral aspect, showing paired nuclei, four pairs of flagella, etc.
b and *b′*. Lateral view, showing sucker-like ventral depressed area. ×
c and *d*. Encysted forms.
e. Degenerated form.
f. Diagram (more highly magnified) showing origins and arrangement of the four pairs of flagella from the paired rod-like organs or axostyles.

and the sinuous line between them often being the first phenomenon to attract attention on microscopical examination (Fig. 198, *d*). Infestation with this parasite is extremely resistant to treatment. It occurs also in rats, mice, rabbits, dogs, cats and sheep.

3. **SPIROCHÆTA.** This term is used for a great number of minute organisms the exact classification of which presents many difficulties. It is convenient to group under the general heading of "Spirochætes" the *Treponema* group of organisms causing **syphilis** and **yaws,** also those responsible for the various forms of **recurrent fever,** including **rat-bite fever,** due to the *Spirillum minus,* and the *Leptospira* of **epidemic jaundice**. The spirochætes are long, thin, wavy, thread-like organisms, mostly actively motile; and the different species show considerable variations in length, thickness, number and character of their undulations or corkscrew-like twists, and method of progression. They multiply by transverse division. They have no nuclei, the chromatin being distributed diffusely throughout their body. Some forms exhibit minute granules in their cytoplasm, and some, *e.g.*, *Treponema duttoni*, assume a "granule-phase" in their intermediate hosts, reappearing later in spirochætal form. In many species, no such transformation has been observed. Only a short description of these organisms need be given here, as they are fully described in Textbooks of Bacteriology.

(i) **Treponema pallidum (Spirochæta pallida)** of **Syphilis.**[1] This organism was first described by Schaudinn and Hoffmann in 1905 as the cause of syphilis. Its average length is about 7 μ, and its width about 0·25 μ, though shorter and longer forms are common. It has some eight or ten fine, regular, deep, spiral twists, the body being prolonged at each end into a fine point. Certain writers consider these spirochætal forms to be merely one stage in the life-history of the parasite, and describe other phases, the existence of which, however, still lacks confirmation. *Tr. pallidum* is found in the primary and secondary lesions, but its demonstration is often difficult in the tertiary. Spirochætes have been detected in the brains of cases of general paresis (pp. 1012–14). *Tr. pallidum* can be inoculated into monkeys, with the production of a primary sore, followed, in about a month, by secondary symptoms. Local lesions can also be produced in the rabbit by inoculation into the eye and testicle.

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[1] *See* Figs. 45 and 611, pp. 80 and 1013.

(ii) **Treponema pertenue (Spirochæta pertenuis)** of **Yaws (Frambœsia)** (p. 88). This organism, which was first described by Castellani in 1905 in scrapings from yaws-pustules, is morphologically indistinguishable from *Tr. pallidum*. Inoculation and immunity-experiments suggest that these two species of spirochæte, and the diseases produced by them, are distinct from one another, although the lesions of both are similar.

(iii) **The Spirochætes** of **Relapsing Fevers (Spirochætosis). Treponema** or **Spirochæta recurrentis** (*Sp. obermeieri* or *Borrelia recurrentis*), the cause of the European variety of this disease, is found in the peripheral blood during the attacks and relapses, but not in the intermissions, of the fever. The infection is carried mainly by lice, especially *Pediculus corporis*—apparently not by the bite of these insects, but by their being crushed on the skin in the process of scratching by the patient, or from their excreta, the spirochætes being thus inoculated into the abrasions (p. 435). Infection can occur also through the conjunctiva, if rubbed with contaminated material. Short (7 to 9 μ) and long (16 to 19 μ) forms, with an average breadth of 0·25 μ, and sometimes still longer variants, occur in the blood. *Spirochæta berbera* (*Tr. berberum*), the cause of North African and Egyptian relapsing fever : *Spirochæta* or *Treponema carteri*, the infective agent of Indian, and probably also of Mesopotamian, relapsing fever : *Sp.* or *Tr. rossii* of East African (carried by the tick, *Ornithodorus moubata*) : and *Sp.* or *Tr. novyi*, the agent of North American, relapsing fever, are all closely allied varieties, which can be distinguished with difficulty from one another by serological and inoculation-tests.

(iv) **Treponema** or **Spirochæta duttoni** of **African Tick-Fever.** This organism closely resembles *Tr. recurrentis*, *Tr. novyi*, and *Tr. carteri* morphologically, and, by some authorities, it is regarded as identical with the two last of these spirochætes. Its usual vector is the tick, *Ornithodorus moubata*, one of the *Argasidæ* (p. 431), the excrement of which carries the infection ; and, in Somaliland and elsewhere, similar ticks, *O. savignyi* and *O. erraticus*, are the probable transmitting agents. After the spirochætes are ingested by the tick, some of them pass through the wall of the gut into the body-cavity fluid, make their way into the cells of certain organs (*e.g.*, the Malpighian tubules), in which they break up into granules or coccoid bodies. These granules may pass to the ovaries, and, by infecting the ova, may be transmitted to the young ticks.

(v) **Leptospira icterohæmorrhagiæ.** This is a spirochæte with very small spirals and recurved, or hooked, ends. "*Leptospira icteroides*," which Noguchi erroneously described as the cause of the virus-produced yellow fever (p. 122), is probably identical with *L. icterohœmorrhagiœ*. There are also non-parasitic forms of *Leptospira* to be found in water (*L. reflexa*), and considerable confusion has arisen from these being mistaken for pathogenic forms. *Leptospira icterohœmorrhagiœ*, the causal agent of **Infectious** or **Infective Jaundice, Spirochætosis Icterohæmorrhagica** (p. 771), also known as **Weil's Disease,** is found in tbe blood, urine, cerebrospinal fluid, and blood-stained sputum in cases of this infection, as well as in the internal organs, especially the liver. Its intermediate host is the rat, in the urine and fæces of which it has been found. The rat thus forms the reservoir of infection—it is stated by Neill that, in the United States, probably some 10 per cent. of all wild rats carry the *L. icterohœmorrhagiœ* in their kidneys, and excrete it in their urine ; infection of rats has also been found in Scotland,[1] France, Belgium, North Africa, etc., and Fullerton detected it in four out of a hundred and one London rats examined (1919) ; but the exact method of transmission of the organism to man, and whether it is conveyed by some insect, or by contaminated food or water, has still to be determined. It may possibly obtain entrance through skin-abrasions, or by way of the mucous membranes. The disease affects especially the liver, which the organism reaches probably by way of the blood-stream. Serum-treatment of the disease has met with considerable success. One attack confers a lasting immunity, and many individuals appear to be naturally immune. Children are most liable to the disease, both sporadic and epidemic. The guineapig is susceptible, and for diagnosis the inoculation into it of blood or urine from a suspected case may be employed. Spirochætal forms of jaundice occurred in France during the War of 1914–18. Its occurrence amongst sewer-workers has also been reported.

(vi) **The spirochæte of rat-bite fever** (called "Sodoku" in Japan, where the condition is common) is a small organism classed as *Spirillum minus* (or *Sp. morsus-muris*), as it has a spiral body with terminal flagella. It is found chiefly in the rat, but other animals, including the cat, may harbour it and transmit the infection from their saliva to man by biting. After an incubation-period of about ten days, there is a febrile reaction with skin-rash and inflammatory reaction at the site of the initial bite. The organism is found in the tissues and blood during the fever.

(vii) **Treponema or Spirochæta vincenti of Fusi-Spirochætal Infections, including Vincent's Disease.** This organism, usually in close association with *B. fusiformis* (*Fusiformis fusiformis*), is the cause of various fusi-spirochætal infections, of which "Vincent's angina" (p. 710 and Fig. 390, p. 709)—or preferably Vincent's disease, as the faucial or tonsillar affection is merely one form of its manifestations—and ulceration of the gums are the most important. The latter—**fusi-spirochætal pyorrhœa**—is extremely common, almost every case of pyorrhœa examined by the authors showing enormous numbers of these two organisms in varying proportions, along with other varieties of spirochætes, leptothrix- and mould-like filaments and mixed cocci and bacilli, including streptococci. The gums are probably the commonest primary site of such infections, which may attack the tonsil (Vincent's angina), palate, cheek and other parts. **Noma** (p. 704) and **agranulocytic** (granulocytopenic) **angina** (pp. 636–7) are important clinical aspects of such infections. These two organisms also occur very frequently in the soft concretions so often found in the tonsillar crypts, and actual ulceration need not necessarily supervene. In such fusi-spirochætal infections, the Wassermann reaction is negative, and, should a positive reaction be obtained, it points to a double infection with this disease and syphilis. The spirochæte is from 12 to 25 μ or more in length, with tapering extremities and comparatively few, usually five or six, wide and often irregular coils or undulations (Fig. 390, p. 709). It is motile, Gram-negative, and anaerobic.

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[1] *See* G. Lovell Gulland and George Buchanan, "Spirochætosis icterohæmorrhagica in East Lothian," *Brit. Med. Jour.*, 1924, i, 313 and G. Buchanan, Special Report Series, No. 113, Medical Research Council, London (1927).

Tropical ulcer, a form of phagedænic ulcer found in India, East Africa, and elsewhere, appears to be due to a spirochæte, sometimes called *Treponema* or *Spirochæta schaudinni*, in association with fusiform bacilli, and usually also with various bacilli and cocci, yeasts, etc. It is now regarded as identical with *Tr. vincenti.*

Similar spirochætes (*Tr. buccalis*, *Tr. dentium*, etc.) are found in the healthy mouth, but more commonly in association with decayed teeth. Many are probably saprophytes. For further details, see general references given and works on Bacteriology.

PARASITES OF THE CLASS SPOROZOA

The main feature of these parasites is that they have, in most species, two cycles of development—a sexual and an asexual. In some forms, *e.g.*, *Eimeria* (causing coccidiosis), these cycles occur in the same host ; in others, *e.g.*, the parasites of malaria, the sexual stage proceeds in an intermediate host, the mosquito. Infestation may be by ingestion, as in coccidiosis, or by bite of the intermediate host, as in the case of malaria. The parasites invade and cause destruction of the cells of the host. The details of the life-cycles will be described under the Malarial Parasites (p. 376).

The Sporozoa are widely distributed in nature, and parasitic forms are common in many animals, vertebrate and invertebrate. Only a few, especially the malarial parasites, are of importance as parasites in man.

Coccidiosis. This is due to an *Eimeria*, usually either *E. perforans*, or *E. stiedæ*, and is common in the rabbit in which it excites proliferative changes in the intestinal and more especially in the bile-duct epithelium, with the production of masses resembling tumours (Fig. 199, p. 376). The parasite is a small ovoid body, 30 to 40 μ by 15 to 20 μ, with a nucleus and capsule. Its sexual and asexual cycles occur in the epithelial cells and re-infection of these is brought about by merozoites.[1] Transmission is by swallowing the oöcysts.

Only a few cases of coccidiosis in man are on record, but, in addition to its occurrence in rabbits, it is a common and serious disease in many other animals, especially in poultry and game-birds (*e.g.*, grouse-disease) in which a fatal enteritis is produced.

Hæmosporidia. This Sub-order of the Class Sporozoa, contains several groups, of which only the Genus *Plasmodium* is of importance in human pathology. It comprises the various Species of malarial parasite. Other Genera, *e.g.*, *Hæmoproteus* (or *Halteridium*) and *Leucocytozoön*, are found in birds.

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[1] "Merozoite": *see* 4th footnote on p. 377.

These parasites infest the blood-corpuscles (*Leucocytozoön* invades the leucocytes, hence its name), causing their destruction. Transmission is by insects—mosquitoes in the case of malaria.

Piroplasms belonging to the Sub-order *Piroplasmidia*, which are non-pigmented, piriform protozoa, infest the blood-corpuscles of certain animals and produce severe anæmia, hæmoglobinuria (the " red-water fever " of sheep, cattle and dogs), and jaundice. Transmission is by various forms of ticks.

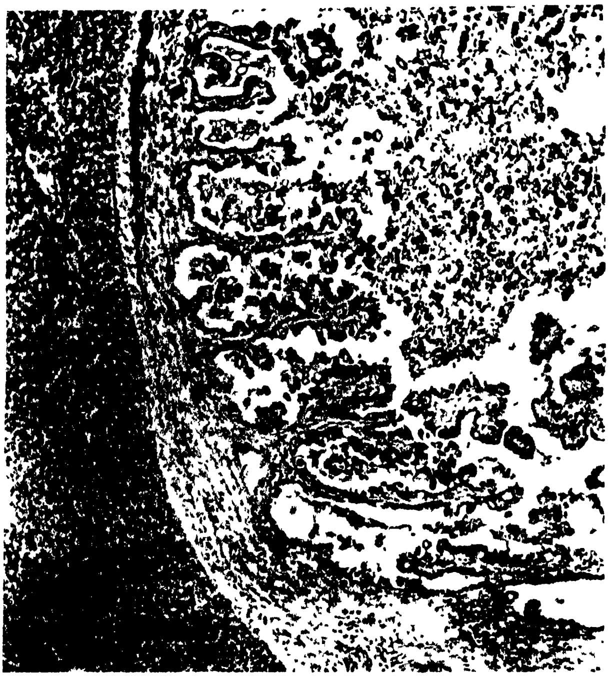

FIG. 199. Liver from a rabbit with coccidiosis, showing adenoma-like structure of cyst. × 60.

MALARIAL PARASITES (Plate XII, opposite p. 378, and Figs. 1, 2 and 3, Plate XIII, opposite p. 380). There are three Species of malarial parasites found in the human subject—*Plasmodium vivax*, the tertian parasite : *Pl. malariæ*, the quartan parasite : *Pl. falciparum* (*Laverania malariæ*), the parasite of tropical, pernicious, or æstivo-autumnal malaria.

They are distinguished from one another both by their morphological characters and their effects upon the host. Each has an endogenous and an exogenous life-cycle, the former within the human host, the latter in the body of a mosquito. The endogenous cycle (schizogony) continues in the blood or in some of the internal organs of the human subject for an indefinite period until the asexual reproductive faculty of the parasite is exhausted, or until the parasite itself has been destroyed by spontaneous natural cure or by artificial medicinal interference ; whilst, in the mosquito, sporogony takes place as a result of conjugation between male and female.

Laveran in 1880 discovered the malarial parasite. Sir Patrick Manson in 1894 suggested the association between the parasite and the mosquito, and in 1897 Sir Ronald Ross, following up Manson's suggestion, demonstrated the complete life-history of the parasite in the mosquito.

PLASMODIUM VIVAX, the parasite of Benign Tertian Malaria (Plate XII, opposite p. 378, Fig. 200 : and Plate XIII, opposite p. 380, Fig. 1). The sporozoites or true spores, derived from the sexual cycle in the mosquito, are introduced into the blood of the human host by the bite of the infested insect.

After inoculation, the small rod-shaped sporozoites [1] become amœboid and can be seen free in the blood lying in close apposition to the envelope of the red corpuscles. Small protoplasmic processes from them penetrate the envelope, and project into the cytoplasm, and gradually the whole sporozoite enters the red corpuscle, in which the young *Pl. vivax* appears as a small, irregularly-rounded mass of protoplasm, clear and apparently structureless, with a chromatin-granule (the nucleus), which stains bright-red with eosin : and, very commonly, a clear, more or less rounded, unstained area near the centre (the "vacuole")—the whole parasite at this stage having somewhat the appearance of a signet-ring. These young trophozoites,[2] as they are now called, gradually enlarge, coming to occupy more and more of the interior of the red corpuscle. As the parasite increases in size, fine granules of brown hæmozoïn-pigment collect in its protoplasm ; whilst the surrounding cytoplasm of the red corpuscle may come to show the characteristic fine red stippling with Schüffner's dots, which may be stained by Leishman's or other modification of the Romanowsky method. At a later stage, the red corpuscle, which has become larger in size and paler in colour, is seen to be occupied by an irregular, actively amœboid mass of protoplasm possessing a nucleus and containing particles of pigment. The amœboid movement gradually ceases and the irregular protoplasmic body is known as the schizont.[3] In a large proportion of the individual parasites, the nucleus now undergoes division, followed by segmentation of the cytoplasm which collects round the nuclear particles, and thus are formed usually sixteen, and occasionally twenty-four, merozoites. The pigment remains about the centre, surrounded by the rosette-like cluster of merozoites,[4] which are minute spherical bodies. During this process of schizogony, the infested corpuscle gradually disintegrates, and, when the process is complete, the merozoites are free in the blood-plasma and the cycle restarts. The residual pigment is taken up by large mononucleated phagocytic cells, and carried by them to various organs and tissues, especially the spleen, liver and bone-marrow, in which it is deposited, producing in them the characteristic malarial pigmentation (p. 228). Some of the wandering merozoites are ingested and digested by leucocytes and other phagocytic cells, but some escape this fate and attack and enter fresh red corpuscles, within which they become the trophozoites of a next generation. The freeing of merozoites takes place every forty-eight hours and coincides with the pyrexial attacks, which thus recur every other day.

As a rule, each affected red corpuscle is invaded by a single parasite, but two or more merozoites may enter one erythrocyte, and each parasite may undergo the complete process of schizogony. Again, a patient may be bitten by infected mosquitoes on successive days, and thus two sets of parasites, each having a forty-eight hours' cycle, may be introduced into his blood. In such a case, merozoites of each set will develop on alternate days, and the pyrexial attack will, in consequence, occur daily.

When the parasites are first introduced into the blood, their number is comparatively small, and they therefore produce no appreciable effect on the host. But multiplication by schizogony goes on, and in from six to twelve days, or more—the so-called incubation period—the parasites are sufficiently numerous to produce, either by direct action, or more probably through the agency of some toxic product, the febrile and other symptoms.

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[1] Sporozoite : from σπόρος, *sporos*, a sowing or seed (formed by sexual union), from σπείρειν, *speirein*, to scatter.

[2] Trophozoite : from τροφός, *trophos*, a feeder, from τρέφειν, *trephein*, to nourish and make to grow.

[3] Schizont : from σχίζειν, *schizein*, to split or divide (without previous sexual union).

[4] Merozoite : from μέρος, *meros*, a part or division, from μείρομαι, *meiromai*, I divide into lots.

The artificial inoculation of benign tertian malaria, either by means of the intravenous injection of blood from a suitable malarial patient or by the bite of infected mosquitoes, is extensively used as a therapeutic measure in cases of general paresis and certain other forms of neurosyphilis (pp. 1011 and 1015).

The **sporonts** are of two kinds, the male and female **gametocytes.**[1] In the male, the nucleus is larger than in the female, and the cytoplasm is free from granules of reserve-material ; whereas, in the female, it is full of such granules. Sporonts can also be distinguished from schizonts by certain characteristics. The full-grown schizont is about 10 μ in diameter, and the nucleus is placed at the periphery of the body. The **female sporont** is 12 to 16 μ in diameter, the nucleus lies at the periphery, the cytoplasm stains deeply, and the grains of pigment are two or three times as large and twice as numerous as those in the schizont. In the **male sporont,** the nucleus is large and is placed near the centre of the body, the cytoplasm stains faintly, whilst the pigment-granules are as well developed as they are in the female. The sporonts are found in the peripheral blood in the later stages, and are taken up in it by the mosquito. The ripe gametocytes (sporonts) are able to resist the digestive juices of the mosquito, and from them, when taken into the stomach of the insect, the formation of gametes commences. In the **male gametocyte,** the nucleus splits up, giving off chromidia, which make their way to the surface of the body of the parasite. With great rapidity, motile threads, four to six in number, are shot out from the protoplasm and appear at the surface of the parasite. These are the **microgametes,** and they contain all the peripheral chromidia. They lash about actively, and eventually become free from the microgametocyte. They are slender, flagella-like bodies, sometimes with a thickened extremity or with multiple thickenings in their course, and consist largely of generative chromatin. In the maturation of the **female gametocyte,** some nuclear substance is eliminated and the cell becomes the **macrogamete.** Each microgamete seeks out and penetrates one of the macrogametes and fuses with its nucleus, and the two elements, by their conjugation, thus form the **zygote,**[2] which enlarges, becomes elongated in form, and develops into a motile individual termed the **vermicule** or **oökinete** (" travelling egg-cell "). The vermicule pushes its way through the epithelial lining of the stomach of the mosquito, and comes to rest in the muscle immediately below its epithelial covering. There it becomes spherical, enlarges and comes eventually to bulge towards or into the body-cavity of the insect, and forms an encysted body, the **oöcyst.** In this the nucleus (synkaryon) undergoes division, and the cytoplasm collects round the daughter-nuclei to form sporoblasts, the containing-structure being now termed the **sporocyst.** In each **sporoblast,** the nucleus divides into a number of smaller nuclei, which travel to the surface of the sporoblast and grow out each into a bud-like or dagger-like projection of protoplasm to form a **sporozoite.** Thus the cyst becomes crowded with sporozoites, varying in number from hundreds to thousands. The ripe

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[1] Gametocyte : from *γαμητέον*, *gamēteon*, " one must marry," from *γαμεῖν*, *gamein*, to marry.

[2] Zygote : from *ζυγωτός*, *zugōtos* or *zygōtos*, yoked or joined, from *ζυγόω*, zugoō or zygoō, I join together.

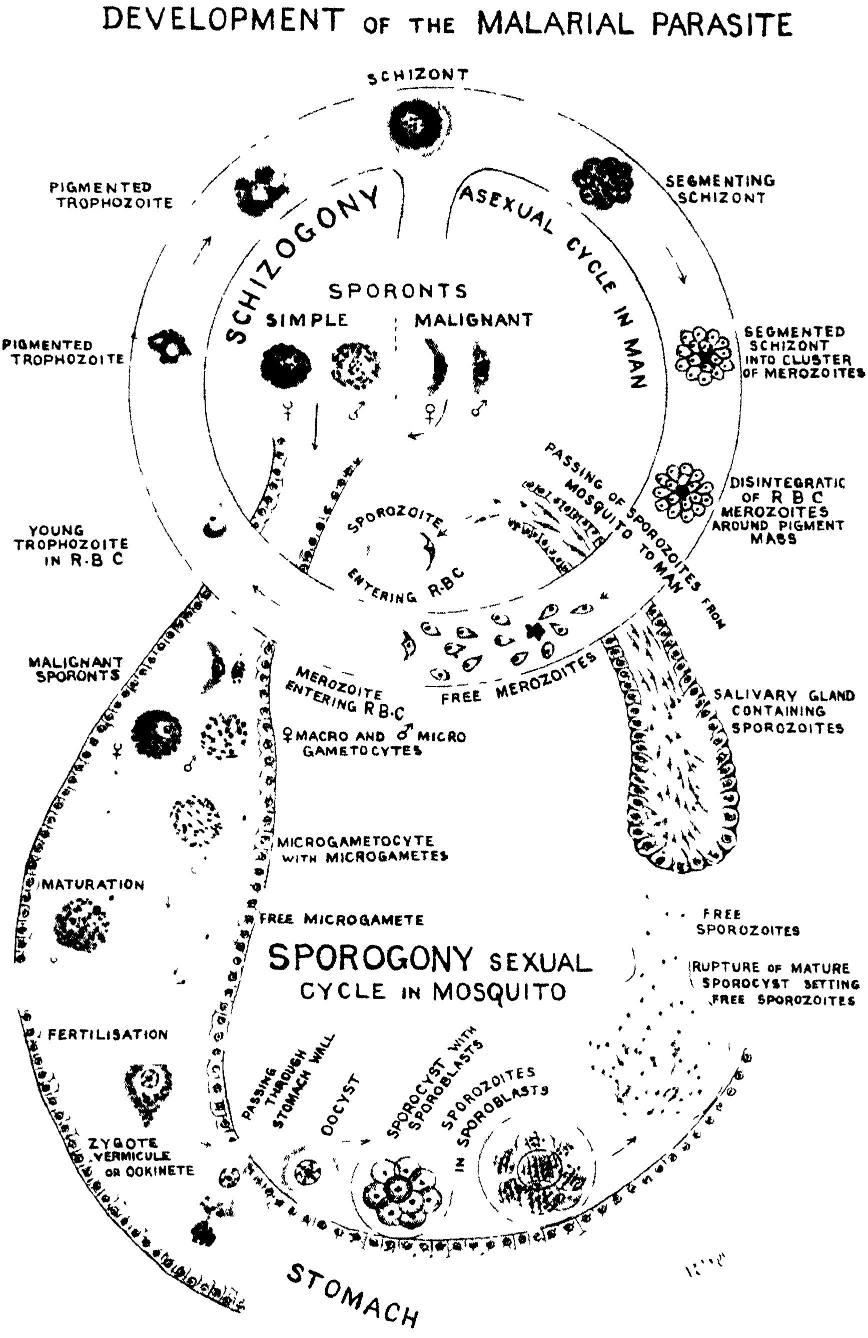
DEVELOPMENT OF THE MALARIAL PARASITE
SCHIZONT
SEGMENTING SCHIZONT
SEGMENTED SCHIZONT INTO CLUSTER OF MEROZOITES
DISINTEGRATIC OF R B C MEROZOITES AROUND PIGMENT MASS
PIGMENTED TROPHOZOITE
PIGMENTED TROPHOZOITE
YOUNG TROPHOZOITE IN R·B C
SCHIZOGONY
ASEXUAL CYCLE IN MAN
SPORONTS
SIMPLE
MALIGNANT
♀
♂
♀
♂
SPOROZOITE ENTERING R.B.C
PASSING OF SPOROZOITES FROM MOSQUITO TO MAN
FREE MEROZOITES
MEROZOITE ENTERING R B·C
♀ MACRO AND ♂ MICRO GAMETOCYTES
MALIGNANT SPORONTS
♀
♂
SALIVARY GLAND CONTAINING SPOROZOITES
MICROGAMETOCYTE WITH MICROGAMETES
MATURATION
FREE MICROGAMETE
FREE SPOROZOITES
SPOROGONY SEXUAL CYCLE IN MOSQUITO
RUPTURE OF MATURE SPOROCYST SETTING FREE SPOROZOITES
FERTILISATION
PASSING THROUGH STOMACH WALL
OOCYST
SPOROCYST WITH SPOROBLASTS
SPOROZOITES IN SPOROBLASTS
ZYGOTE VERMICULE OR OOKINETE
STOMACH

FIG. 200. Semi-diagrammatic representation of the development and life cycle of the malarial parasite—chiefly of *Plasmodium vivax*, the crescentic gametocytes of *Pl. falciparum* being introduced *in parallel* for completeness. For details *see* text.

sporocyst now ruptures into the body-cavity of the mosquito, the sporozoites are set free into the blood-fluid of the insect and pass into various parts, but especially into the salivary gland, in which they accumulate in enormous numbers. When the mosquito again bites its vertebrate host, the sporozoites pass down in the salivary secretion, which is injected, through the proboscis, into the blood of that host, in which they enter the red corpuscles and grow to form schizonts, or later, sporonts. The entire development within the body of the mosquito lasts some ten or twelve days. In Fig. 200, Plate XII, opposite p. 378, will be found, in semi-diagrammatic form, a schematic representation of these two cycles of schizogony and sporogony, as they occur in man and the mosquito respectively.

PLASMODIUM MALARIÆ, the parasite of Quartan Malaria (Plate XIII, Fig. 2, opposite p. 380). The parasite of quartan fever is less actively amœboid than that of the tertian form ; the " vacuole " disappears early ; the contained pigment is relatively prominent ; the pigment-granules are coarser, appear earlier,

DIFFERENTIAL CHARACTERS OF THE HUMAN MALARIAL PARASITES
(Fantham, Stephens and Theobald[1])

Character.	*Plasmodium malariæ* (Quartan).	*Plasmodium vivax* (Benign Tertian).	*Plasmodium falciparum* (Malignant Tertian)
Schizogony.	Complete in 72 hours.	Complete in 48 hours.	Complete in 48 hours or less.
Trophozoite	Smaller than *P. vivax* ; larger than *P. falciparum*. Pseudopodia not marked or long.	Young trophozoite, large. Long pseudopodia.	Young trophozoite, small.
Movements.	Rather slow in immature forms.	Active amœboid movements.	Sometimes actively motile.
Pigment	Coarse granules, peripherally arranged ; little movement.	Fine granules, with active movement.	Granules fine, and scanty ; movement oscillatory.
Schizont	Smaller than red corpuscle.	Larger than red blood-corpuscle.	Smaller than red corpuscle.
Merozoites .	6 to 12 forming rosette.	16 to 24 regularly arranged.	8 to 32 (according to different authors) arranged irregularly.
Gametocytes	Spherical.	Spherical.	Crescentic.
Distribution of parasites in vertebrate host.	About equal numbers in peripheral and visceral blood.	Larger numbers in visceral blood.	Scanty in peripheral blood compared with the enormous numbers in the internal organs. The latter part of the cycle (schizogony) may occur in the internal organs only.
Alterations in erythrocytes.	Corpuscle almost normal.	Pale and hypertrophied. Schüffner's dots seen in deeply-stained specimens.	Corpuscle may be shrunken and dark, or may be colourless. Maurer's coarse dots sometimes seen.

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[1] From " Animal Parasites of Man," London (1916), p. 171.

and tend to lie towards the periphery. The infested blood-corpuscles do not become enlarged, but remain unaltered or even become smaller than normal. Development takes place, as in the tertian parasite, both by schizogony and by sporogony. In the former, *i.e.*, the asexual cycle, the merozoites are more regular in arrangement than in the tertian parasite, six to nine, or even twelve, merozoites being formed in each schizont, grouped in a definite rosette-, daisy-, or wheel-like fashion. The merozoite-formation takes place every seventy-two hours, the pyrexial attack recurring every three days.

PLASMODIUM FALCIPARUM (*Laverania malariæ*), **the parasite of Tropical or Pernicious or Subtertian Malaria, or Æstivo-Autumnal Fever** (Plate XIII, Fig. 3, opposite). This organism, in its early intracorpuscular stage, is also ring-like, but is smaller in size than the parasites of the benign tertian and quartan types. Not infrequently two or even more of these small signet-ring forms are found in one red corpuscle. Fully-grown forms, which are usually scanty or absent in the peripheral blood, attain a size of only half or two-thirds the diameter of the erythrocytes, which tend to shrink and have a "brassy colour," and occasionally show coarse stippling (Maurer's dots). The most characteristic forms in the peripheral blood are the crescentic gametocytes or "crescents," with centrally-placed pigment.

Schizogony takes place at irregular intervals of time, mainly in the spleen, the bone-marrow, and the capillaries of the brain. Sporulating forms are rarely found in the peripheral blood, but are numerous in spleen-juice withdrawn by puncture during an attack. In the sporulating forms, the merozoites are variously stated at ten or twelve (Manson), eight to twenty-four, with an average of twelve to sixteen (Fantham, Stephens, and Theobald), or thirty-two (J. G. and D. Thomson, from observations on cultures and spleen-films). Sporogony takes place and corresponds with what has been described for *Plasmodium vivax*. The male sporont is sausage- or crescent-shaped, with scattered pigment-granules; the female is also crescent-shaped, but the pigment-granules tend to be more aggregated round the nucleus. The sporonts average 9 to 14 μ in length, and 2 to 3 μ in thickness. When taken into the stomach of the mosquito, the crescents become first ovoid and then spherical, and correspond with the gametocytes of *Plasmodium vivax.*

The Cultivation of Malarial Parasites. The schizogony-cycle of development has been successfully reproduced artificially *in vitro,* glucose (dextrose) being added to the infested blood, which is then defibrinated, the fibrin removed, and the blood, thus treated, being then incubated at 37° to 41° C. J. G. and D. Thomson,[1] from their observations upon such "cultures," give the numbers of merozoites formed under such conditions as :—

Pl. vivax : sixteen—occasionally more.
Pl. malariæ : eight.
Pl. falciparum : thirty-two in maximum segmentation.

Mosquitoes and Malaria. The developmental cycle of the parasites in the mosquito has already been described, and it may be said generally that this

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[1] "Annals of Tropical Medicine and Parasitology" (1912), **6**, p. 449, and (1913), **7**, pp. 153 and 509.

DESCRIPTION OF PLATE XIII

PLATE XIII

Fig. 1. The asexual cycle of the parasite (*Plasmodium vivax*) of **Simple Tertian Malaria.**

a. The merozoites freed from the red corpuscle and becoming scattered. Note mass of pigment.
b. c. The young amœboid parasites (merozoites) entering the red corpuscles and becoming trophozoites.
d. The parasite (trophozoite) in the corpuscle. The nucleus (red) and the unstained central vacuole are shown.
e. f. g. Stages showing gradual increase in size of the trophozoite, with accumulation of pigment in its protoplasm. The infested red corpuscles are also increased in size.
h. A further stage, in which the parasite almost fills the red corpuscle. The pigment has accumulated at the centre, and the chromatin-granule has become divided into numerous scattered particles.
i. j. k. Various stages in the segmentation of the parasite (segmenting schizonts) by which the merozoites are formed.
l. Microgametocyte (male sporont).
m. Macrogametocyte (female sporont).
n. Amœboid mononucleated cell which has ingested some of the pigment.
×1000

Fig. 2. Film of blood from a case of **Quartan Malaria** showing various stages in the asexual life-cycle of the parasite (*Plasmodium malariæ*).

k. Polymorphonuclear leucocyte.
a. b. Young trophozoites in red corpuscle.
c. d. e. f. More advanced trophozoites.
g. h. Forms showing segmentation.
i. Merozoites with central mass of pigment.
×1000

Fig. 3. Film of blood from a case of **Pernicious Malaria** (*Plasmodium falciparum*).

a. Free merozoite.
b. c. Merozoite entering red corpuscle.
d. Merozoites (ring-form of parasite) in red corpuscles.
d′. A red corpuscle containing two parasites.
e. e′. Microgametocyte or male sporont in red corpuscle.
f. Macrogametocyte or female sporont in red corpuscle.
g. Mononucleated cell.
h. Blood-platelets, not to be confused with free merozoites (*a*). ×1000

Fig. 4. **Phagocytosis.**

a. Polymorphonuclear leucocyte containing several ingested diplococci.
b. Polymorphonuclear leucocyte which has ingested numerous bacilli.
c. Polymorphonuclear leucocyte which has ingested a red corpuscle.
d. Mononucleated cell with pseudopodia projected around a polymorphonuclear leucocyte which it is in the act of ingesting.
e. Mononucleated cell which has ingested a leucocyte and a red corpuscle.
f. Mononucleated cell from the bone-marrow, which has ingested numerous leucocytes, which are seen in various stages of disintegration (digestion). (pp. 616–7.)
g. Large mononucleated phagocytic cell from the bone-marrow, showing irregular pseudopodia and ingestion of polymorphs.
h. A large mononucleated cell from the bone-marrow, containing numerous red corpuscles (from a case of untreated Addisonian anæmia).
×1000

Note.—In Fig. 4, these mononucleated cells belong to the reticulo-endothelial system of cells.

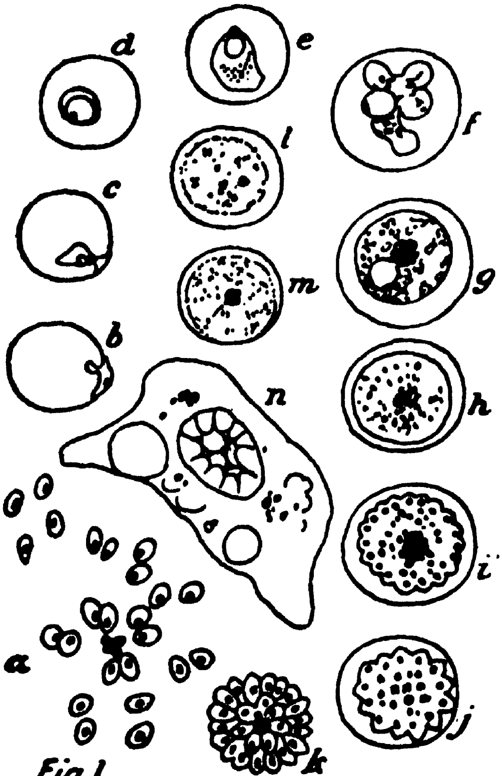

Fig. 1.

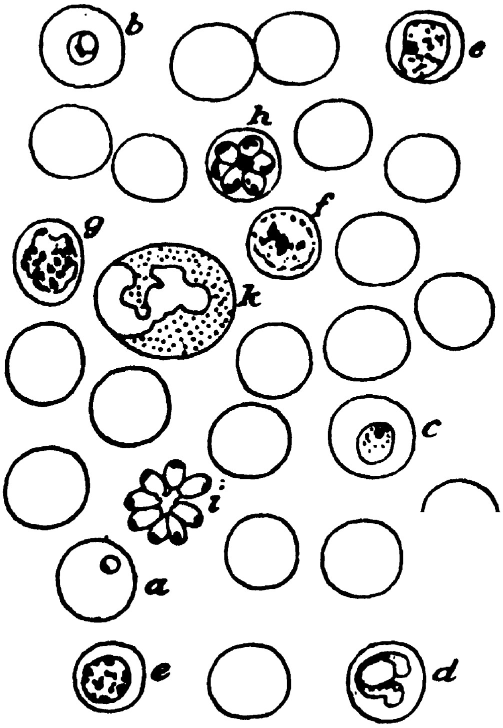

Fig. 2

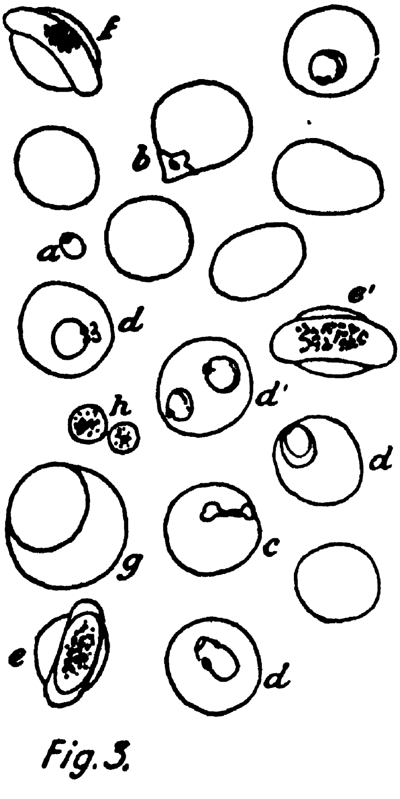

Fig. 3.

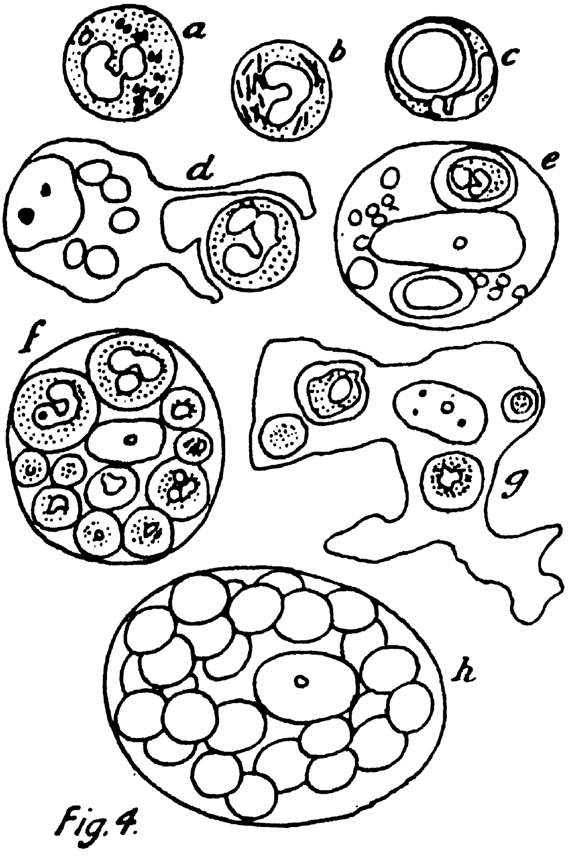

Fig. 4.

PLATE XIII, p. 380.

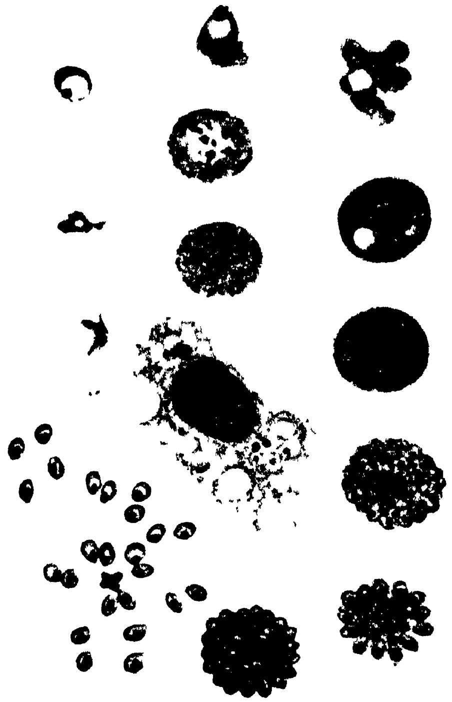

FIG. 1. × 1000

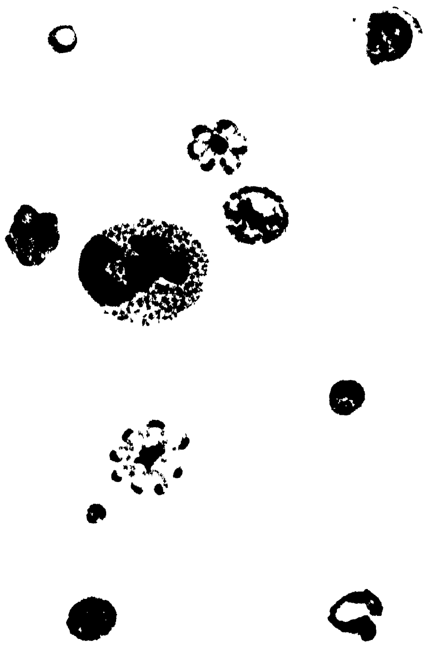

FIG. 2. × 1000

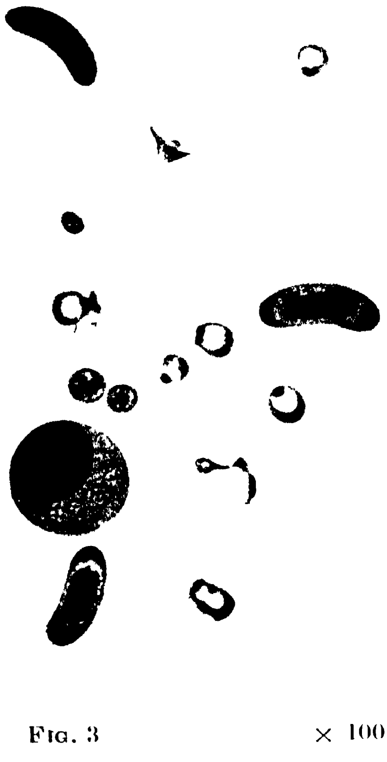

FIG. 3 × 1000

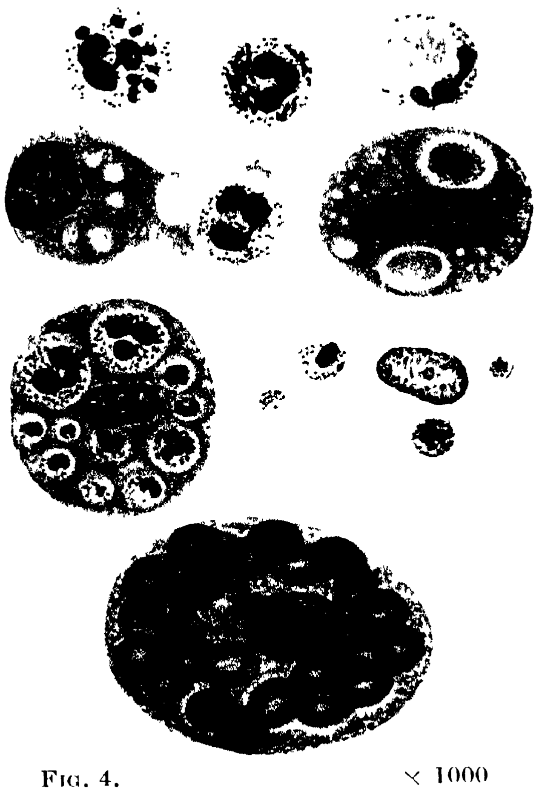

FIG. 4. × 1000

host is necessary to preserve the life of the species. It is true that, in certain cases of malaria, after long intervals and without re-infection, relapses occur. In these patients, the parasites are probably present in the body in small numbers, insufficient to cause clinical symptoms, but any factor which causes lowered resistance allows the parasites to multiply more freely and produce the symptoms of the relapse. It has been proved conclusively by experiment that the development of the parasite takes place in the stomach-wall of certain mosquitoes belonging to the genus *Anopheles*,[1] and that healthy persons can be inoculated by the bite of these infested mosquitoes—a method also now utilised for the therapeutic inoculation of patients suffering from general paresis (pp. 1011 and 1015). Preventive measures designed to interfere with the breeding of mosquitoes serve to render a malarial area free from infestation.

Pathological Anatomy. The blood-changes have already been partially described while dealing with the parasites of malaria. The anæmia may be of all degrees up to the most profound. It is characterised, not only by the destruction of the erythrocytes and their consequent reduction in numbers, but also by diminution in the hæmoglobin of the surviving corpuscles. Anisocytosis, or irregularity in size, is practically always found. The presence of Schüffner's and Maurer's dots in the infested corpuscles has already been described, and a varying degree of punctate basiphilia is also common in a number of the other corpuscles. There is usually a **leucopenia,** with a relative increase of the large mononuclears, which are specially active in the destruction of the parasites. In a fresh-wet film of the blood examined on the warm stage, these cells may be seen englobing and digesting the parasites, whether the latter are free or contained within red corpuscles. Hæmozoïn-pigment may be found in their cytoplasm, derived both from the parasites so ingested and from the residual pigment freed on the breaking-up of schizonts into their component merozoites. This process of phagocytosis of parasites and pigment is also actively carried on by the reticulo-endothelial cells, especially in the spleen-pulp, bone-marrow, liver, mesentery, and intestinal mucosa, another important site of this process being the capillaries of the brain, especially in malignant tertian infestations characterised by coma and other cerebral symptoms. The capillaries of these organs and tissues may also show large numbers of infested red corpuscles in their lumen—sometimes so numerous and closely packed as to plug and obstruct them. J. G. Thomson has demonstrated in culture how the infested blood-corpuscles tend to adhere around macrophages, forming a mass which is thus capable of blocking capillaries. The **pigmentation** of various organs and tissues, so characteristic of malaria, is usually best seen in the spleen, bone-marrow and liver, and is derived largely from the black hæmozoïn so taken up ; but yellow or yellowish-brown hæmosiderin, originating from the hæmoglobin of destroyed red corpuscles, is also stored in these positions, as in other serious anæmias. Bilirubin is present in excess in the blood and there is usually a moderate degree of acidosis. The total bulk of the blood is also diminished, a point of importance in interpreting the blood-count. The **spleen** is enlarged, and, in acute cases, almost diffluent. With repeated attacks, it may become greatly enlarged, and the fibrous trabeculæ and vascular sheaths may show great thickening; whilst the phagocytic and blood-destructive activity of the pulp-cells (pp. 691 and 695), which often attain a large size and may contain numbers of infested or damaged red corpuscles, is very marked. The enlarged malarial spleen is more liable to rupture (pp. 690, 695 and 759). The **bone-marrow** is dark red and congested, and shows erythroblastic transformation, as well as the pigmentation already described; and, in heavy infestations and old-standing cases, degenerative changes may supervene. Parasites are often very numerous in the spleen and bone-marrow, even when absent from the peripheral blood; and various phases of their life-history may take place only in these.

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[1] The following list of Anopheline Mosquitoes, which act as Malaria-Carriers, is given in the official *Memoranda on Medical Diseases in the Tropical and Sub-Tropical War Areas* (1919), p. 158 : "*Anopheles maculipennis, palestinensis, superpictus, bifurcatus, turkhudi, stephensi, funestus*, and *costalis* are well-known vectors. *A. pharoensis, pulcherrimus* and *squamosus* are effective, but probably only to a small extent." (For fuller lists and geographical distribution, *see* books mentioned at beginning of this chapter.)

The **liver** is usually enlarged. Parasites may be found in the erythrocytes contained in the capillaries, and in the endothelial cells lining these. Focal necrosis may occur; and, in long-standing cases, cirrhosis has been found (p. 774). The **kidneys** do not usually show any specific changes, but both acute and chronic nephritis have been described as a result of malarial infestation. For the occurrence of hæmoglobinuria in malaria ("blackwater fever") *see* p. 659. In malignant tertian cases dying in coma, the **brain** may show small hæmorrhages and areas of necrosis, the results of capillary blockage. In the severe cases with **gastro-intestinal** symptoms, there may be scattered patches of necrosis and hæmorrhage in the gastro-intestinal mucosa, also the result of capillary blockage. The other organs, apart from the deposit of pigment, have no specially characteristic pathological features.

The Neosporidia. In this group of Sporozoa is placed the *Sarcocystis* (Rainey's and Miescher's Tubes), a common parasite of animals, but very rarely recorded in man. The sarcocysts live in muscle, sometimes forming definite nodules. *Rhinosporidium seeberi* (or *R. kinealyi*) was formerly placed in this group, but is now regarded as a vegetable fungus (pp. 95 and 503). It lies usually between the connective-tissue cells and is recorded as occurring in the nose, naso-pharynx, uvula, conjunctiva, lacrimal sac, ear and penis of man. It occurs in India, Ceylon, Argentina, and North America. The late Professor Ashworth, of Edinburgh, to whose paper readers are referred for a detailed description, placed it among the lower fungi (Phycomycetes), and not with the Sporozoa. A full list of references up to 1923 is given in his paper.[1]

Intracellular Bodies. Many minute organisms are found, in various diseased conditions, either in the cytoplasm or within the nuclei of cells. Some of these are of importance in human disease, *e.g.*, the *Rickettsias* (of typhus, Rocky-Mountain spotted fever, and trench-fever), which are transmitted by lice or ticks. Others, *e.g.*, *Bartonella*, are rare in man. These are described in works on Parasitology and Bacteriology, which should be consulted for further information.

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[1] *Transactions of the Royal Society of Edinburgh* (1923), **53,** Part II (No. 16), pp. 301–342. *See* also our footnote on p. 95.

SECTION II

METAZOA. INVERTEBRATA

VERMES, HELMINTHES OR WORMS[1]

PLATYHELMINTHES OR FLAT-WORMS

The **Platyhelminthes** are flattened, bilaterally symmetrical worms, leaf-shaped (*e.g.* the **Trematoda**) or tape-like (*e.g.*, the **Cestoda**) in outline. The integument consists of a cuticle with glandular cells, beneath which lies the subcuticular, cellular, or "parenchymatous" layer, in which are embedded the nervous system and the excretory apparatus. Under these lies the musculo-dermal layer, whilst between this and the alimentary canal is the cellular "mesenchymatous" tissue, containing the sexual glands and other organs if present. The Cestodes or Tapeworms do not possess any alimentary canal; whilst, in the Trematodes or Flukes, this is represented by the mouth, the muscular pharynx, and the mid-gut, which is usually forked. There is generally no hind-gut or anus.

All the Cestodes and the great majority of the Trematodes are hermaphrodite.

TREMATODA OR FLUKES

These are usually flattened, leaf-shaped, unsegmented worms (Figs. 202–3), the adults being parasitic in vertebrates, and the intermediate larval forms in some species of mollusc. The adults are mostly hermaphrodite (except *Schistosoma hæmatobium*, *S. mansoni* and a few others), and the male and the female organs open near one another on the ventral surface in the middle line, usually towards the anterior end, either in front of or behind the ventral sucker—the position of the genital pore varying, however, in different species.

Life-Cycle of the Trematodes.[2] The Common Liver-fluke (*Fasciola hepatica*) of the sheep may be taken as the type. From the ova when mature, if these are deposited in water, the embryo hatches out and gives rise to a free-swimming, somewhat elongated, ciliated organism known as the **miracidium.** This enters its special intermediate host, a small water-snail, usually *Limnœa truncatula*, which is very common in ponds and ditches. In the body of this mollusc it enlarges, and becomes a hollow, gutless, elongated sac or germinal tube, the **sporocyst,** within which are developed either other sporocysts, or what are known as **rediæ**—minute, somewhat elongated, cylindrical larval organisms, possessing a sac-like alimentary canal. The sporocyst then ruptures, and the contained sporocysts or rediæ escape into other parts of the snail. The formation of sporocysts and rediæ may be repeated, but eventually the rediæ proceed to develop within themselves certain actively motile, round bodies—**cercariæ**—which possess a forked gut, two suckers, a rudder-like tail, and also a special boring-spine situated in the oral sucker. These cercariæ, which are the characteristic **larval stage,** make their way out of the body of the snail into water, attach themselves to grass or some aquatic plant, cast off their motile tails and boring-apparatus and become encysted, waiting there until they are taken into the body of their definitive host, probably by the ingestion by the latter of the contaminated vegetable matter or drinking water containing these encysted forms. They then develop into the adult fluke, finding their way from the intestine into the bile-ducts and liver, and occasionally into the portal vein and elsewhere. The life-history of the other fluke-worms is probably similar, but in many cases has not yet been fully worked out. In some forms, the cercariæ penetrate into the body of a second intermediate molluscan host and become encysted, until, together with their host, they are ingested by a suitable definitive or terminal host.

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[1] For classification, life-histories, etc., of parasites in this section *see* Fantham, "Animal Parasites of Man" (1916), Stephens and Theobald, London; and E. Brumpt, "Précis de Parasitologie" (1936), Masson et Cie, Paris.

[2] For the derivation of the word "Trematode," *see* footnote on p. 712: and of "Cestode," on p. 393.

There are many families of fluke-worms, but only a relatively small number are known to be parasitic in man. Some of these are found also in domestic and wild animals, which have, in addition, species of worms specific to themselves.

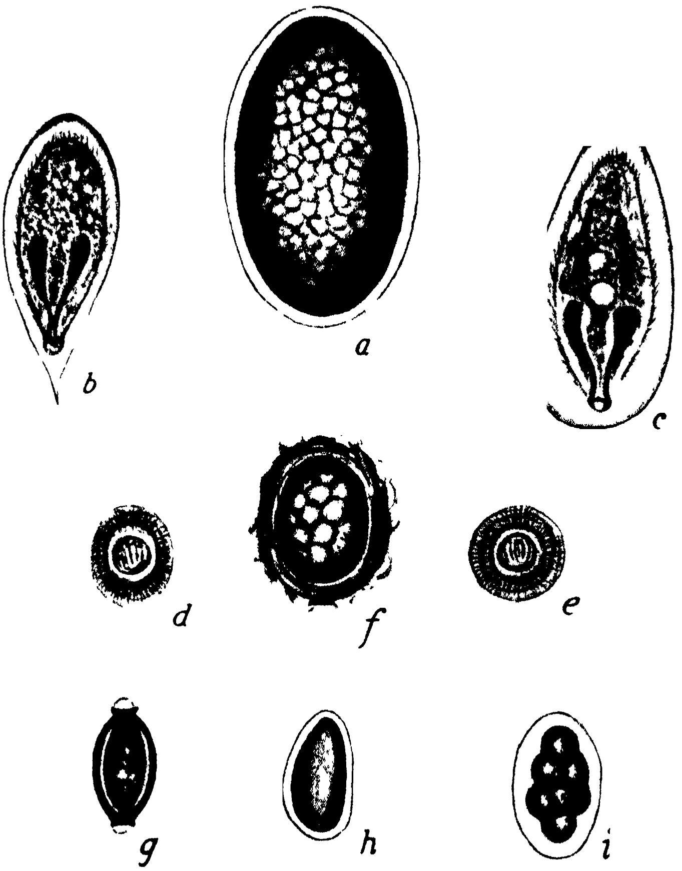

Fig. 201. Ova of some of the commoner parasitic worms (each division on scale corresponds to 0·1 mm. = 100 μ). × 250. For descriptions *see* text.

- *a. Fasciola hepatica*, the common liver-fluke (p. 384).
- *b. Schistosoma hæmatobium* from urine (p. 386).
- *c. Schistosoma mansoni* from fæces (p. 391).
- *d. Tænia saginata* or beef-tapeworm (Oncosphere from fæces) (p. 397).
- *e. Tænia solium* or pork-tapeworm (Oncosphere from fæces) (p. 394).
- *f. Ascaris lumbricoides*, the common round-worm (p. 408).
- *g. Trichuris trichiura* (*Trichocephalus trichiuris* or *T. dispar*) or whip-worm (p. 416).
- *h. Enterobius* or *Oxyuris vermicularis* or thread-worm (p. 409).
- *i. Ankylostoma duodenale* or hook-worm (p. 411).

In the hermaphrodite group of trematodes several species are pathogenic to man.

FASCIOLA HEPATICA (Syn. *Distoma* or *Distomum hepaticum*; *F. humana*, etc.). The **liver-fluke** is a common endo-parasite of sheep, deer, cattle and other herbivorous animals, and is found only rarely in man. It inhabits the bile-ducts and, in the human subject, it occasionally finds its way into the portal vein and elsewhere, and has been described as causing abscess-like subcutaneous swellings. In sheep it is the cause of liver-rot, a very fatal disease—characterised by fever, emaciation, anæmia, ascites and œdema—which may occur in epidemics in infested districts at certain seasons, especially towards the end of summer. The liver first becomes enlarged and later undergoes consecutive atrophy, the bile-ducts becoming enormously dilated into irregular sacs containing the flukes. In man, if only a few parasites are present, the results may be trifling; but serious abdominal symptoms such as gastro-intestinal disturbance accompanied by jaundice and perhaps ascites may occur. A fatal issue is rare. The condition may be diagnosed by finding the ova on microscopical examination of the fæces or, less commonly, by the passage of the adult *per anum*. In North Lebanon, a peculiar affection, due to the eating of raw infested liver and known as *Halzoun*, is described, in which the adult fluke becomes attached to the pharynx or neighbouring parts, giving rise to inflammation and swelling, with resulting symptoms, and even death. Vomiting may occur and bring about the dislodgment and expulsion of the worm, with recovery.

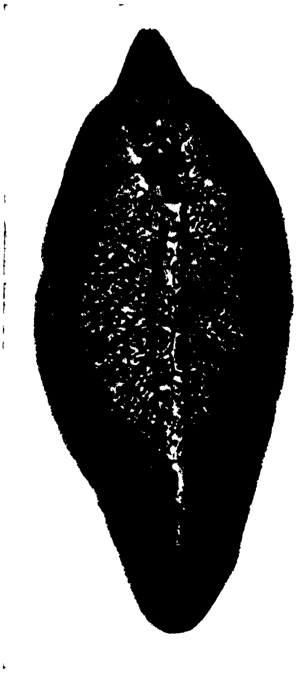

Fig. 202. *Fasciola hepatica* or liver-fluke. × 2½.

Morphology. The adult fluke is leaf- or lancet-shaped, with a conical anterior extremity, at which is placed the oral sucker. The genital orifice is situated between the two suckers immediately in front of the ventral non-perforate sucker. The length varies from 20–30 mm., and the breadth from 8–13 mm., the worm being often curled like a leaf with the concavity ventrally. The parasite is pale yellowish or slightly brownish-white in colour, with occasionally a delicate pale blue or rose-pink tint.

The ova (Fig. 201, *a*, opposite) are brown or brownish-yellow in colour, and are ovoid in shape, with a terminal operculum. They measure about 130 by 70 μ in diameter, and may show segmentation. The later development of these has been described on p. 383.

FASCIOLOPSIS BUSKI (Syn. *Distoma* or *Distomum buski*, *D. crassum*). This is one of the largest fluke-worms parasitic in man, measuring 30 to 70 mm. in length by 14 or 15 mm. in width. It inhabits the human intestine, causing diarrhœa. There is anæmia of varying degree, œdema and extreme apathy. It has been found in Eastern and Southern Asia, where it is a common parasite of the pig.

CLONORCHIS SINENSIS (Syn. *Opisthorcis sinensis*), and the nearly related **OPISTHORCIS FELINEUS** are found in China and Japan, India and in Europe, especially Russia, their habitat being the gall-bladder and bile-ducts of the dog and cat, as well as of man. The intermediate hosts are fish.

PARAGONIMUS RINGERI (Syn. *Distoma ringeri*, *D. pulmonale*, *D. pulmonis*): **P. WESTERMANII** (Syn. *D. westermanii*, *Mesogonimus westermanii*): and **P. KELLICOTTI** are closely allied **lung-flukes**, and are regarded as identical by some writers *P. ringeri* has been found in the human subject in China, Japan, Korea and neighbouring countries, especially in mountainous districts, where it is the cause of parasitic or endemic hæmoptysis. The body of the parasite is somewhat more rounded and less flattened than the majority of fluke-worms. It is pale reddish-brown in colour, and measures 8 to 10 mm. in length and 4 to 6 mm. in breadth and thickness. The genital orifice is situated near the posterior margin of the ventral sucker. The eggs are ovoid, brownish-yellow, thin-shelled and operculated, and their average longitudinal and transverse diameters are 80 and 50 μ respectively. In the human subject these parasites are found singly or more usually in pairs, within cyst-like cavities about the size of hazel-nuts, with thick connective-tissue walls, associated with the bronchi. The flukes may burrow in the lung-substance, especially near the surface under the pleura, and may, by penetrating the walls of the vessels, give rise to **hæmoptysis.** This parasite is also found in the brain (probably by embolic spread from the primary lung-lesion—producing convulsions, paralysis, cerebral softening, etc.), eyelids and orbit, pleura, liver, intestinal wall, peritoneum, cervical lymph-nodes, scrotum and other sites. The lung-condition may be diagnosed by finding the characteristic ova on microscopical examination of the muco-purulent rusty or blood-stained sputum. When passed, the yolk usually does not show segmentation; but, if incubated in water, a ciliated miracidium may be hatched after an interval of a couple of weeks or more. It enters a mollusc of the Genus *Melania* in which it develops in the usual way to a cercaria which enters the body of a fresh-water crab or a crayfish and there encysts in the muscles. When eaten by dog, cat, or man, the parasite becomes free, perforates the intestine and finds its way through the abdominal and thoracic cavities to the lungs. *P. westermanii* has been found in the Bengal tiger (captive specimens which died in Amsterdam and Hamburg zoological gardens), and *P. kellicotti* in the pig, dog and cat in North America. These lung-flukes are covered with small movable spines, the grouping and shape of these, it is said, constituting characters by which the three species may be differentiated.

HETEROPHYES HETEROPHYES (Syn. *Cotylogonimus*, *Distomum*, *Mesogonimus* or *Cœnogonimus heterophyes*). This is the smallest fluke-worm known, measuring about 2 mm. in length by 1 mm. or less in breadth. It is rare, and has been found in the human subject in Egypt, Japan and elsewhere.

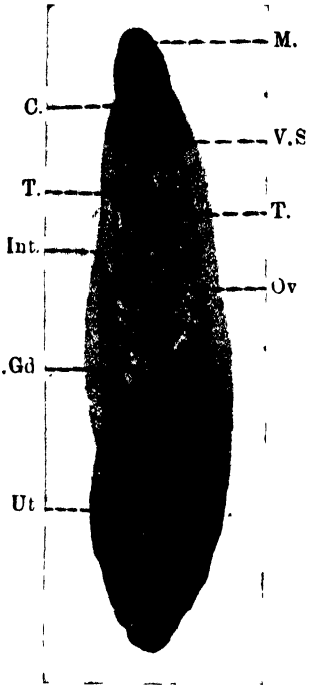

FIG. 203. *Dicrocœlium lanceatum.* (To illustrate morphology and structure of a Trematode.) M., mouth surrounded by oral sucker; C., cirrhus recess; V.S., ventral sucker; T.T., testes; Int., forked cæcal intestinal canal; Ov., ovarian gland; Y.Gd. yolk gland; Ut., uterine tubes. × 10.

THE SCHISTOSOMIDÆ

These resemble the preceding hermaphrodite parasites in general structure, but are bisexual. The males are broader and shorter than the females, and possess thin lateral edges, which curl ventrally to form the so-called gynæcophoric canal which encloses the female (Figs. 207, 208). The latter is slender and thread-like, and is usually darker in colour than the male. *S. hæmatobium*, *S. mansoni* and *S. japonicum* are the important pathogenic members of this Family of Blood-Flukes.

SCHISTOSOMA HÆMATOBIUM (Syn. *Distoma* or *Distomum hæmatobium*, *Bilharzia hæmatobia*). This parasite is the cause of one form of **Schistosomiasis** or **Bilharziasis**—endemic hæmaturia, sometimes known as Egyptian hæmaturia (" Egyptian chlorosis ") from the frequency of its occurrence in Egypt, although it is also common in Abyssinia, the Sudan, South Africa, and elsewhere in the African continent. In Egypt, where the ova of the worm have been identified in the mummies of the Pharaohs, the incidence of the disease varies in different districts. It is most intense in the neighbourhood of the Nile and in irrigated areas ; and in certain districts as many as 90 per cent. of the native population are infested. Cases in India and other parts of Asia have also been reported, and its sporadic occurrence has been noted in many other localities.

Morphology. The male measures 12 to 14 mm. in length and, when the lateral edges are in-rolled, 0·4 to 0·5 mm. in diameter, though, when flattened out, it is about 1 mm. broad at its widest point, just behind the ventral sucker. It is white in colour. The oral and ventral suckers are placed close together at the anterior end, the genital aperture being situated in the middle line immediately behind the ventral sucker and at the beginning of the gynæcophoric canal. On account of the curling of the lateral edges of the body the worm has a cylindrical appearance, instead of the leaf-like shape characteristic of the trematodes. The outer or dorsal aspect of the body is covered with innumerable minute spine-like papillæ, which aid in the locomotion of the parasite within the veins. There are also delicate spines on the suckers, and others of larger size throughout the inner surface of the gynæcophoric canal. The bifurcation of the intestine occurs immediately in front of the ventral sucker, but usually reunion into a single median trunk takes place more posteriorly, to form a single short gut-stem. There are four (or five) large somewhat angular testes. The female is about twice the length of the male (*i.e.*, about 20 mm.), and is more filiform, with tapering extremities, its average diameter being about 0·25 mm. The anterior extremity, with its two suckers, is white in colour ; whilst the posterior part is greyish and contains the reunited intestine, which runs in a zigzag manner to the posterior extremity and, if filled with ingested blood, shows as a dark-reddish or brownish line. The outer surface of the female worm is for the most part smooth, unlike that of the male upon which it largely depends for migration. There are delicate spines on the suckers, and larger spines at the posterior extremity. The ovary occupies the posterior half of the body, and the uterus is long and voluminous and contains numerous terminally spined ova. The ova (Figs. 201, *b* and 204) are of a characteristic elliptical or lemon shape. They are non-operculated, pale-yellowish in colour, and possess a thin transparent shell with a minute sharp thorn-like spine at the posterior extremity—in contradistinction to its position in the ova of *S. mansoni*, where, instead of being terminal, this spine is placed slightly towards the lateral aspect of the extremity of the ovum (Fig. 201, *c*, p. 384). The ova of *S. hæmatobium* vary considerably in size—120 to 150 μ in length by 40 to 60 μ in breadth.

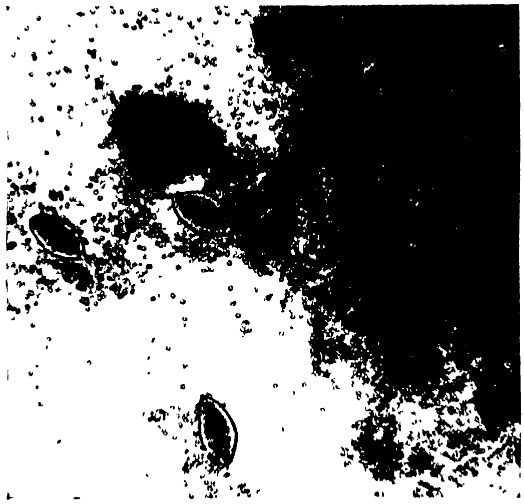

FIG. 204. Ova of *Schistosoma hæmatobium* and red blood-corpuscles in urine. × 60.

Before these worms reach maturity, they live apart in the veins of the liver, but as they become more mature they are found united in pairs in the portal vein, from which they migrate—the male carrying the female in the gynæcophoric canal—to the pelvic veins, especially the vesical, in which position maturity is attained. The ova are deposited chiefly in the small veins of the submucous tissue of the bladder, and, owing to the alternate contraction and relaxation of its walls, they are gradually moved through the tissues until they reach the interior of the organ, along with the contents of which they are expelled from the body of their host. At this stage the ova may show advanced segmentation, or more usually they contain the fully-formed ciliated miracidium; and, if placed in water on a microscopical slide and kept suitably warmed, the shell may be seen to split longitudinally, liberating the actively motile free-swimming miracidium. The intermediate host has been identified by Leiper[1] as the small, whelk-like water-snail, *Bullinus*, especially *B. contortus* (Fig. 205), and also the very similar *B. dybowski* and *B. innesi*, in which the miracidium becomes a sporocyst. This gives rise to numerous daughter-sporocysts, which in turn produce enormous numbers of bifid-tailed cercariæ (Fig. 206); these then escape into the surrounding water, and constitute the agent by which man becomes infested. In a test-tube of infested water they are just visible to the naked eye as a swarming mass of very minute, white, hair-like bodies. These cercariæ consist of a body possessing an anterior and a ventral sucker (corresponding to those of the adult worm), a number of secretory "poison-cells," and a tail with a terminal bifurcation. They do not possess eye-spots or a muscular pharynx. The infested snail continues to discharge large numbers of these cercariæ for several weeks. They can

FIG. 205. *Bullinus contortus*, the whelk-like water-snail which acts as the intermediate host of *Schistosoma hæmatobium*. (Natural size.)

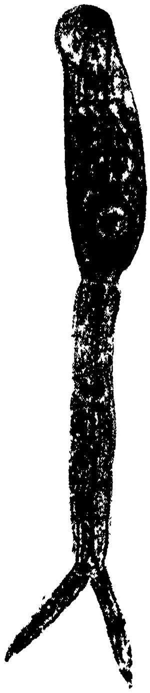

FIG. 206. Bifid-tailed cercaria of *Schistosoma hæmatobium* from liver of *Bullinus contortus*. × 200.

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[1] Report of the Bilharzia Mission in Egypt, 1915, *Journal of the Royal Army Medical Corps*, London (1918), **30**.

penetrate the unbroken human skin (not infrequently giving rise to considerable and sometimes intense irritation[1]), or the buccal and nasal mucous membranes ; make their way into the blood-vessels, especially the small veins, and probably also into lymphatics ; and are then carried by the blood-stream to the liver, where they develop into the adult worms—the whole process taking about a couple of months. If the cercariæ fail to obtain access to their human host, they perish in from thirty-six to forty-eight hours. Man may therefore become infested by bathing, wading and washing in, or drinking, such contaminated waters, unless they are thoroughly filtered, boiled, treated with suitable chemicals, or (if free from infested snails) stored for forty-eight hours or longer.

Incidence. In Egypt, the disease attacks specially workers on the flooded land and children who play in infected water. In South Africa, it is commoner in boys than in girls. The periodic occurrence of the disease in Lower Egypt shows a distinct relationship to the annual flooding of the Nile. The climate must be sufficiently warm to allow of the survival and hatching out of the miracidium, which is easily killed by exposure to cold.

The course of the disease may be divided into two stages : (1) the **toxæmic stage**, supervening in from four to ten weeks after infestation, and characterised by fever, abdominal pain, enlargement and tenderness of the liver and spleen, emaciation, urticaria, eosinophilia (usually considerable, but occasionally slight, or even absent); whilst in the serum a positive complement-fixation reaction may be elicited with an antigen prepared from the livers of infested snails : followed, after a latent period of anything between six weeks to two and a half years, by (2) the **localised lesions** of **vesical schistosomiasis (bilharziasis),** characterised, in addition to the clinical symptoms of urethral, penile, or perineal pain, urgency and frequency of micturition, etc., by hæmaturia, which may be more or less constant, intermittent, or irregular. The mucous membrane of the bladder shows congestion, swelling and catarrh, often with the presence of white submucous nodules, and later, perhaps, septic cystitis with the subsequent production of "sandy patches," the mucosa looking "as if it were impregnated with a fine, brownish or yellowish powder (myriads of ova). This is accompanied by a gradual hypertrophy and new formation of connective tissue, so that dry, hard or plate-like patches with this sandy appearance arise ; the thickening eventually affects all the coats of the bladder."[2] The bladder-wall may become much thickened and infiltrated by fibrous tissue, suggesting, in some cases, the fibrosis of slowly developing malignant disease, and there may also be present peculiar wart-like excrescences or papilloma-like outgrowths. In these and in the thickened tissues numerous ova can be found ; and, by the presence of the ova in the urine, diagnosis can be made with certainty. The uterus, pelvis of the kidney and the kidney itself may be involved, as may also the prostate, vesiculæ seminales and urethra. Urethral and perineal fistulæ are common and malignant disease is a not infrequent sequel.

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[1] **Schistosome-dermatitis,** "water-itch," "swimmer's" or "bather's itch," can be caused also by the cercariæ of various other schistosomes, of which man is not the "normal" host, and is acquired by bathing in waters inhabited by infested snails, *e.g.*, *Limnœa stagnalis*, or *Stagnicola emarginata*, which harbour *C. ocellata*, *C. elvæ*, *C. stagnicolæ*, and other cercariæ of which the adult schistosomes have mostly still to be identified.

[2] Fantham, Stephens and Theobald, "Animal Parasites of Man," (1916), p. 275.

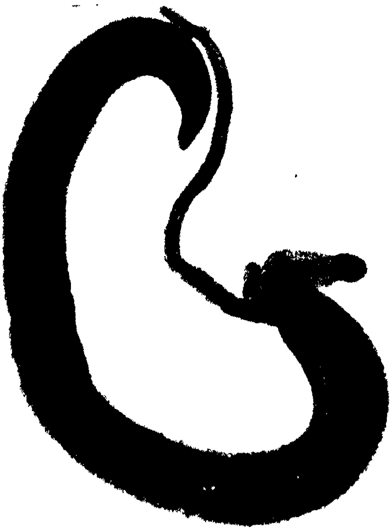

FIG. 207. *Schistosoma mansoni.* A pair of the worms—the narrower filiform female lying in the gynæcophoric canal of the male, the two suckers at the anterior end of which are shown. × 20.

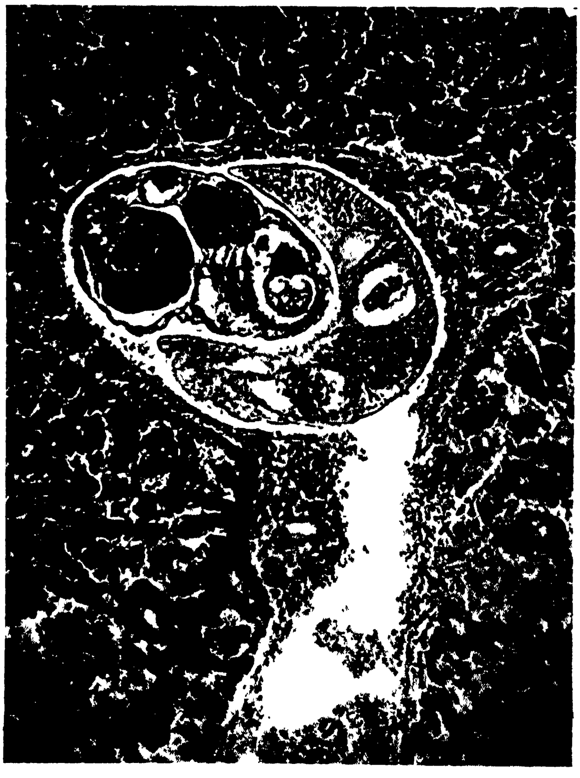

FIG. 208. Transverse section of the paired worms lying in a portal vein in the liver of an experimentally inoculated monkey, showing the female partially enveloped in the gynæcophoric canal of the male, the latter being crescentic in section in this region. × 140.

The liver exhibits considerable proliferation of the fibrous tissue of the portal tracts, and much of the liver-substance may be replaced by dense nodules of fibrous tissue (Fig. 208 opposite, and *cf.* p. 775 and Fig. 433). In female patients, the vagina, and also the vulva and cervix uteri, in addition to the bladder, are liable to be the seat of inflammation and later of condyloma-like overgrowths.

In the later stages, the blood-picture differs from that found earlier in the disease. There is a moderate leucocytosis, averaging about 10,000 per c.mm., though a considerably higher count may be found, especially where there is superadded sepsis. The eosinophilia, which in the earlier toxic stage may be as much as 50 per cent., gradually decreases, the average case showing perhaps some 13 or 14 per cent., and dropping during the two subsequent years to an average of 11 per cent., with a corresponding relative and absolute increase of the ordinary neutrophil polymorphs. A moderate degree of secondary anæmia supervenes, becoming more and more severe as the disease advances. Among infested native Egyptians, according to Fairley, the high case-mortality of about 10 per cent. is largely caused by three factors : "mechanical obstruction by bilharzial granulation tissue, secondary septic infection, and malignant supervention." [1]

SCHISTOSOMA MANSONI (Syn. *Bilharzia mansoni*). This Blood-Fluke, the cause of **Intestinal Schistosomiasis** or **Bilharziasis** (p. 758), was by many regarded, mainly owing to the writings of Looss, as merely a variant of *S. hæmatobium*. It has now, however, been proved by Manson, Sambon, and by Leiper, to constitute a distinct species. It resembles *S. hæmatobium* so closely that reference need be made here only to certain points in which it differs from the latter. The male possesses eight (seven to nine, according to Leiper) small spherical testes ; the divisions of the gut unite well forward, with the production of a very long gut-stem ; and the anterior edges of the lateral walls of the gynæcophoric canal arise more suddenly—almost at right angles—from the anterior portion of the worm, instead of the gradual transition seen in *S. hæmatobium*. In the female, the ovary lies in the anterior half of the body, which tapers gradually instead of ending abruptly as in *S. hæmatobium*, and the uterus is very short. The lateral situation of the spines of the ova (Fig. 201, *c*, p. 384) constitutes the most important distinction in the diagnosis of this type of schistosomiasis. Only one such mature lateral-spined ovum at a time is present in the uterus. Clinically, these ova are found—often, however, with considerable difficulty—in the fæces of infested patients. They may sometimes be demonstrated in scrapings from the bases of the intestinal ulcers in cases where examination of the fæces alone has failed to reveal their presence. The habitat of the paired worms (*e.g.*, in experimentally-infested monkeys) is the inferior and superior mesenteric veins and the portal veins of the liver. The liver is enlarged and congested. The sub-peritoneal coat of the colon may

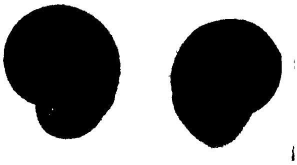

FIG. 209. *Planorbis boissyi*, the ammonite-like carrier of [illegible]
(Natural size.)

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[1] Fairley, *loc. cit.*, p. 1018.

be studded with minute nodules containing ova, and the mucous membrane may show varying grades of inflammation—from congestion and catarrh, minute ulcers, and scattered bilharzial nodules up to extensive sloughing and ulceration, massive pedunculated submucous growths of highly vascular granulation-tissue, and extensive infiltration of the subserous and peritoneal coats. These layers, especially the submucous coat, in which ova are generally most numerous, show endophlebitis, whilst the muscular coats are comparatively little affected.

The molluscan carrier of *S. mansoni* is the small, ammonite-like water-snail, *Planorbis boissyi* (Fig. 209), from which the cercariæ are discharged, the method of infestation of both snail and man being similar to the process already described for *S. hæmatobium.*

Double infestations with both *S. hæmatobium* and *S. mansoni* are not uncommon; and it should also be noted that, in single infestations with one of these alone, although *S. hæmatobium* causes mainly a urinary infestation, its terminally-spined ova may sometimes be found on thorough search of the fæces; and, similarly, the laterally-spined ova of *S. mansoni*, though the infestation is usually preponderatingly intestinal, are occasionally also found in the urine.

SCHISTOSOMA JAPONICUM (Syn. *S. cattoi*, *Bilharzia japonica*). This worm as a parasite in man was discovered in 1904 by Katsurada and, later in the same year, was described by Catto, who found it in a Chinese. It was found by the former observer also in dogs, cats, and cattle, in those districts of Japan where an endemic form of human schistosomiasis—katayama disease—characterised by enlargement of the liver and spleen, cachexia, ascites, and diarrhœa, existed. This worm closely resembles *S. hæmatobium*, but is smaller in size; the body of the male is smooth, not tuberculated, and contains six to eight irregularly elliptical testes in the anterior part of the hind-body. In the female, the uterus occupies almost half the hind-body, showing a narrow lumen which may contain from 50 to 300 soft immature ova. When mature, the latter are ovoid or rounded-ovoid in shape, of a faint yellow tint, with a double contour. They may possess a small lateral spine or minute rounded knob-like projection, analogous to the spine in *S. mansoni.* When this is small or absent, these eggs closely resemble those of *Ankylostoma duodenale,* for which they may be mistaken. The habitat of the adult worm is the smaller mesenteric veins and portal vein; and the resulting lesions are chiefly intestinal, and are analogous to those produced by *S. mansoni* in Egypt, the bladder usually remaining free of infestation. The ovum gives rise to a ciliated miracidium, which infests the intermediate molluscan host, *Katayama* (Syn. *Oncomelania*) *nosophora,* in which the development through various stages to cercariæ occurs.

Egyptian Splenomegaly (pp. 695 and 700). This condition, common in Egypt, and in other countries where schistosomiasis is endemic, may be caused by infestation either with *S. mansoni* or *S. japonicum.* It is due probably to heavy infestation with the parasites which, by their toxic products, cause irritation and proliferation in the spleen as well as to portal stasis from the cirrhotic changes in the liver. It is slowly produced, several years being required before the spleen becomes large, firm and fibrous, meanwhile the liver has reached a stage of atrophic cirrhosis (*see also* p. 698).

CESTODA OR TAPEWORMS

These are endoparasitic, flattened, tape- or ribbon-like worms which do not possess an alimentary canal. The mature stage of the worm is passed in the gastro-intestinal tract— usually of vertebrates— the small intestine being its most frequent habitat. The immature, or larval, stage occurs mainly in tissues, often within viscera. The adult tapeworm consists of a scolex [1] or head and a varying number of semi-independent segments or proglottides,[2] attached to one another and forming the tape-like or chain-like body or strobila (Figs. 210 to 227).

The scolex is very small in size, being usually just visible to the naked eye. It is equipped with four disc- or cup-like, or in some cases two groove-like, suckers. It may be provided with clinging- and boring-organs or hooklets, which vary considerably in number and in arrangement in the different genera. These hooklets are arranged either in a single or in a double circle around the protractile rostellum or beak-like anterior extremity of the scolex, in the manner of a rosette or crown.

The posterior narrow part of the scolex, where it becomes continuous with the strobila,[3] is usually termed the " neck " of the worm. As the strobila is formed by a process of serial budding from the scolex, the most distant proglottides are the largest and most mature, whilst those nearest the scolex are small, and form a slender chain of immature segments. The proglottides vary in different species from a few in number up to several thousands. In practically all the Cestodes, the mature segments are hermaphrodite, each possessing a complete set of male and female generative organs. The form of the uterus is of importance for purposes of identification, and will be described while dealing with the individual species of worms.

Tapeworms of different species vary enormously in length, *e.g.*, from 3 mm. up to as much as 9 or 10 metres or more.

The surface is covered by a cuticle, lying upon the parenchymatous basal membrane, beneath which is the dermo-muscular tube. The interior of each segment is occupied by parenchyma in which are embedded the sexual organs, muscular and nerve-bundles, together with certain concentrically laminated calcareous bodies. The excretory organs resemble those of the Trematodes.

DEVELOPMENT OF CESTODES.[4] As the proglottides become gravid and the uterus within each becomes distended with fertilised ova, they break off from the strobila —singly or in small groups and are passed with the fæces or in some cases they actively make their way out by the anus.

The ova are spherical or slightly ovoid in shape, brownish or yellowish in colour, and possess a thin delicate shell, which, except in the case of *Diphyllobothrium* (Syn. *Dibothriocephalus*), is non-operculated in the more important varieties.

Embryonal development occurs usually while the ovum is still within the uterus, but it may take place immediately after its discharge. Segmentation takes place, and two envelopes are formed around the embryo. The outer of these, the investing envelope or integument, remains attached to the interior of the delicate shell, and is left behind on hatching. The inner envelope or embryonal shell (embryophore) is sometimes, as in the case of the free-swimming embryo of *Diphyllobothrium*, covered with cilia, but is composed more commonly of radially-arranged calcified rod-like bodies, which produce its characteristic striate appearance. In the interior of this lies the embryo, which has now developed into a rounded or perhaps slightly elongated body, armed with three pairs of hooklets. This oncosphere[5] or hexacanth, as the six-hooklotted embryo is now called, on leaving the intestine of the definitive host, may be discharged through the " birth-pore " or uterine aperture, or may be freed by the ultimate rupture or disintegration of the distended proglottis in which it is contained.

CYSTICERCUS or " BLADDER-WORM " LARVAL STAGE. After ingestion by a suitable intermediate host, the embryonal shell or envelope is dissolved off and the active six-hookletted embryo proceeds to bore through the intestinal wall. By way of the lymphatics or by the mesenteric veins it reaches the liver, which in the case of *Echinococcus granulosus* (Syn. *T. echinococcus*) forms the special habitat of the bladder-worm stage. In other instances the embryos travel from the liver—probably by way of the blood-stream—to the muscles or other tissues of the host's body. In whatever situation it is finally lodged, the embryo settles down and becomes passive, loses its hooklets and undergoes distension with fluid in the case of the tapeworms classified as Cystici (*e.g. Tænia solium*, *T. saginata*, and others), thus forming a cyst and entering upon the larval bladder-worm or cysticercus stage of its development. In certain tapeworms, this cystic formation is very slight and rudimentary. In others—the Echinococci—the oncosphere becomes enormously distended, and, by proliferation of its cellular internal germinal layer or endocyst, either other endogenous secondary or daughter-cysts are formed, or "brood-capsules" develop and form scolices. In yet others—the Plerocerci—the embryo or oncosphere develops into a solid larval form, elongated, tape-like or ovoid, with the head invaginated, and this larval form, termed a "plerocercoid," appears to become directly transformed, without cyst-formation and metamorphosis, into the scolex of the adult worm; and a certain degree of budding of proglottides may occur even while the parasite is still within the tissues of the intermediate host—sexual maturity, however, not being reached without the usual transference to the intestine of the final host. This form of development occurs in the case of *Diphyllobothrium*, in which the worm may attain a length of 30 mm. in the intermediate host before such transference occurs.

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[1] *σκώληξ*, *skōlēx*, a worm.

[2] *προγλωσσίς* or *προγλωττίς*, *proglōssis* or *proglōttis*, the point of the tongue, hence tongue-shaped.

[3] *στρόβῑλος*, *strobilos*, something that twists and turns, from *στρέφειν*, *strephein*, to twist and turn, to wriggle. The word also came to mean a (twisted) pine-cone, and hence it acquired the additional meaning of *segmented* like a pine-cone. *στροβίλη*, *strobilē*, modern Latin *strobila*, came to signify a plug of lint twisted into the shape of a fir-cone, and, secondarily, a segmented tapeworm.

[4] "Cestode," like a *κεστός*, *kestos*, a girdle or strap.

[5] "Oncosphere," from Greek, *ὄγκος*, *onkos* (*oncos*), a barb (of an arrow).

DEVELOPMENT OF THE LARVAL SCOLEX INTO THE ADULT WORM. No further development of the larval cysticercus can now occur until the tissues of the intermediate host in which it is embedded are eaten by the final host, in whose intestinal canal all the parts of the cysticercus except the scolex are digested off, the scolex becoming evaginated or turned inside out like the finger of a glove, the suckers being therefore now situated externally as in the adult worm. By means of its suckers and hooklets, if both of these varieties of organ are present, it attaches itself to the intestinal wall of its host, usually in the region of the duodenum or upper part of the jejunum; and it then proceeds to produce the series of proglottides which, together with the scolex, form the adult tapeworm.

Although there are many varieties of tapeworms which are parasitic in the lower animals, some of which occasionally attack the human subject, only four are of special importance as parasites in man, three of these passing their adult stage, and the fourth—*Echinococcus granulosus* (Syn. *Tænia echinococcus*)—its immature stage, in man. The three adult forms are *Tænia solium*, *Tænia saginata*, and *Diphyllobothrium latum*.

TÆNIA SOLIUM, the **Armed** or **Pork-Tapeworm.** The average length of this worm is about 2 to 3½ metres, though it may occasionally be as much as double these dimensions. The scolex, which resembles the head of a small pin in shape, is generally rather less than 1 mm. in diameter, and possesses a retractile terminal rostellum, a double crown of hooklets—alternately larger and smaller in size, and usually just under thirty in number—and four disc-like suckers. The neck is filiform. The strobila consists of 800 or 900 proglottides, which gradually increase in size as they recede from the head. When mature, they are oblong, the longitudinal diameter being considerably greater than the transverse (averaging about 10 by 5 mm.). The uterus is composed of a median longitudinal trunk with seven to ten transversely-placed lateral offshoots possessing numerous secondary diverticula. The genital orifice is marginal, usually slightly behind the centre of each segment, and alternates with comparative

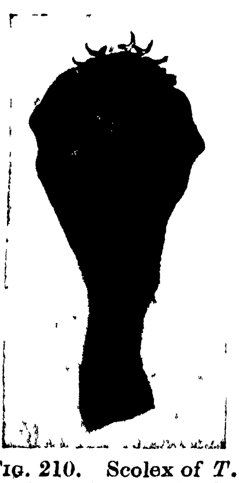
FIG. 210. Scolex of *T. solium*, showing hooklets and suckers. × 24.

regularity in successive segments. The ova are thin-shelled, and the oncospheres (Fig. 211) are surrounded by a thick, symmetrically rounded, brownish or brownish-yellow, radially-striated embryonal envelope (embryophore), measuring 30 to 36 μ in diameter, the globular six-hookletted oncosphere in its interior being about 20 μ in diameter. The segments, which are less motile than those of *T. saginata*, tend to be

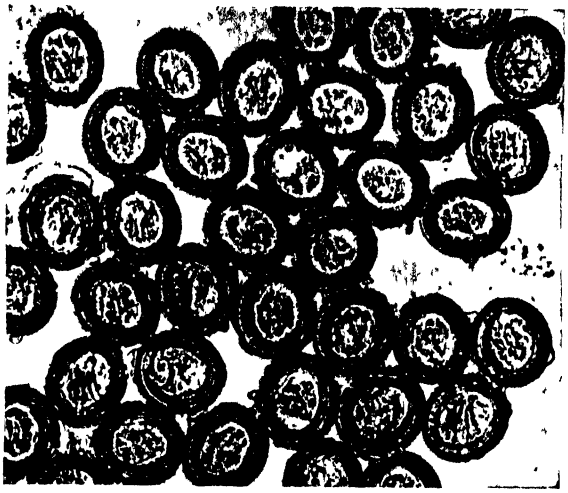

Fig. 211. Oncospheres of *T. solium*, showing radially-striated embryonal envelope or embryophore, and globular six-hookletted embryo or oncosphere. × 300.

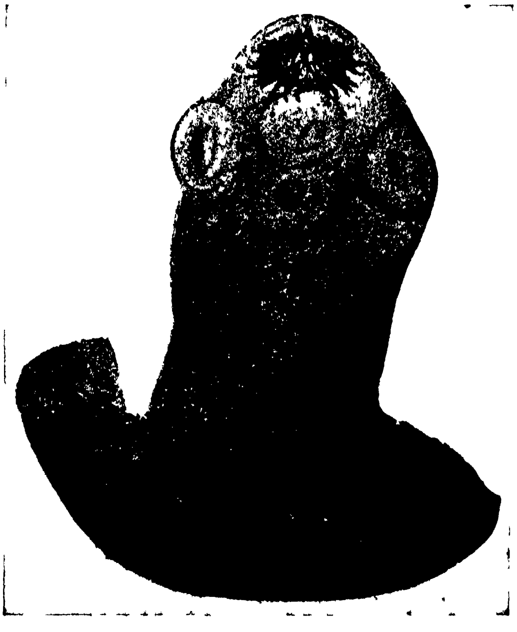

Fig. 212 Cysticercus cellulosæ or bladder-worm stage of *T. solium*, showing development of scolex equipped with hooklets and four suckers. × 32.

voided from the intestine in short chains. In its mature stage, *T. solium* is found only in man ; the immature, larval, or cysticercus stage—the so-called cysticercus cellulosæ—occurring especially in the intramuscular connective tissue of the pig, and less commonly in other mammals. In the pig the condition is known as "measly pork," the cysticerci forming little elliptical bladder-like vesicles, which càn be seen easily with the naked eye, their average length being about 8 or 10 mm. **Cysticercosis** may occur also in man, not only in **muscle** but in the **skin** and **subcutaneous tissue,** where the cysticerci may be present in large numbers, and in various organs, especially the eye and the **brain.** In the brain (Fig. 741, p. 1151), the cysts may attain a considerable size, and may develop numerous diverticula, for which reason they have been termed the **Cysticercus "racemosus," "botryoides,"** or **"multilocularis."** They may

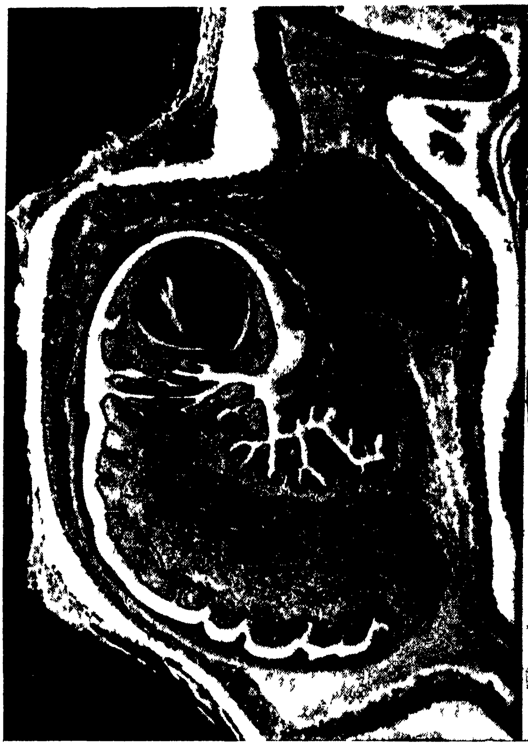

FIG. 213. *Cysticercosis of the brain* section through one of the bladder-worms of *Tænia solium* from the case illustrated in Fig 744, p 1153, showing the scolex developed from, and lying within, the invagination of the wall of the bladder, which in turn has been derived from the main caudal vesicle or bladder from which the larva obtains its name The lumen and outer wall of this vesicle are seen to the left, surrounded externally by the (darkly stained) fibrous tissue capsule derived from the tissues of the host. Mallory's connective-tissue stain. × 25

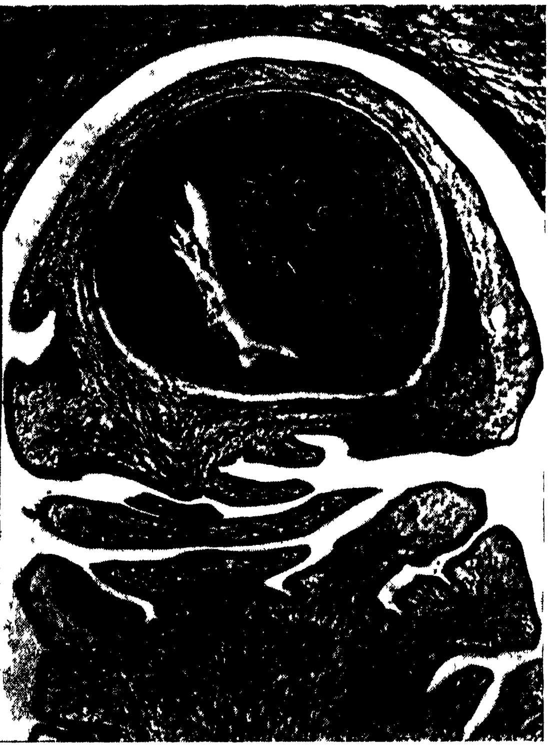

FIG. 214 Higher magnification of anterior end of the scolex shown in Fig 213 The section has passed obliquely through the muscular rostellum with its double circlet of hooklets, and through two of the four suckers. (Dr. Worster Drought's case, W.E.H.) Mallory's stain for connective-tissue. × 80.

(Figs 213–14 are reproduced by kind permission of the Editor of the *Lancet* see footnote on p. 1151 and Figs 741–4, pp. 1151–3) become calcified and thus be demonstrable by X-ray. They may cause epileptic fits, as has been pointed out by MacArthur (1933–4, *see* p. 1151) in the case of soldiers in India,[1] or death by obstruction of the ventricular system with internal hydrocephalus. In the **eye,** cysticerci have been known to persist for as long as twenty years. Such infestations may originate either from the patient himself, if harbouring the adult worm in his intestine, or are, more usually, a fresh infection from without. MacArthur has pointed out that the presence of cysticerci in the brain may not lead to serious symptoms until they die and degenerate (Figs. 743 and 744, pp. 1152–3), the cyst then tending to swell from imbibition of fluid, with resulting pressure upon neighbouring structures.

Usually, man becomes infested by eating imperfectly cooked "measly" pork, the cysticerci of which develop into the adult worms in his intestine (Fig. 215).

Tænia solium is as widely distributed as the pig and is common in certain parts of Germany, France, and Italy, but is seldom found now in Britain, and naturally rare in those Eastern countries in which pork is not eaten.

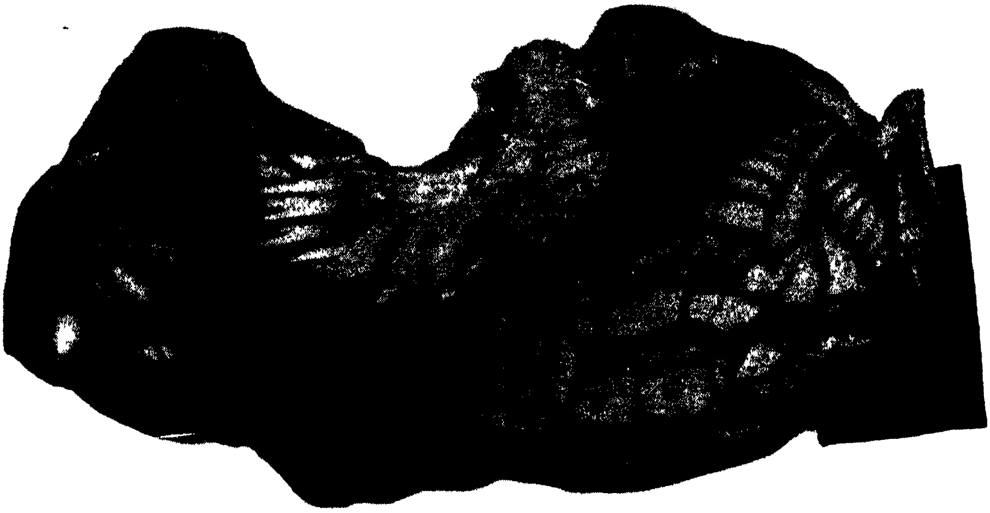

FIG. 215. A mass of tapeworms (*T. saginata*) in human small intestine. Several heads with adjacent small, immature segments are displayed on right against the black background.

TÆNIA SAGINATA—(Syn. *T. mediocanellata, T. inermis*)—the **unarmed** or **beef-tapeworm**—is usually longer than the pork-tapeworm, its average length being from 4 to 10 metres. As a rule, only one parasite is found, whilst in the case of *T. solium* several adult worms may be present at one time in the intestine of the same patient—man being the specific final host of both varieties.

The scolex is cuboidal in shape, measuring 1·5 to 2 mm. in diameter. It possesses four cup-like suckers, but no rostellum or hooklets. The

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[1] *Loc. cit.* (*see* footnote on p. 1151).

proglottides usually number over a thousand, gradually increasing in size on passing backwards, and, as they mature, coming to measure 16 to 20 mm. in length by 4 to 7 mm. in breadth. The genital pore is marginal, opening slightly behind the centre of each segment, and alternating irregularly. The centrally-placed uterine trunk gives off from twenty to thirty-five transverse lateral branches, which in turn may show a few secondary subdivisions. The segments are more muscular and motile than those of *T. solium*. They may leave the intestine singly or in short chains. The ova are rounded and thin-shelled, and contain an oncosphere with a radially-striated embryonal investment closely resembling that of **T. solium**, except for the fact that, in the case of *T. saginata,* it is usually slightly ovoid (30 or 40 by 20 or 30 μ in diameter), whereas the oncosphere of the pork-tapeworm is more nearly spherical in shape (Fig. 201, *d* and *e*, p. 384 : and Fig. 211, p. 395).

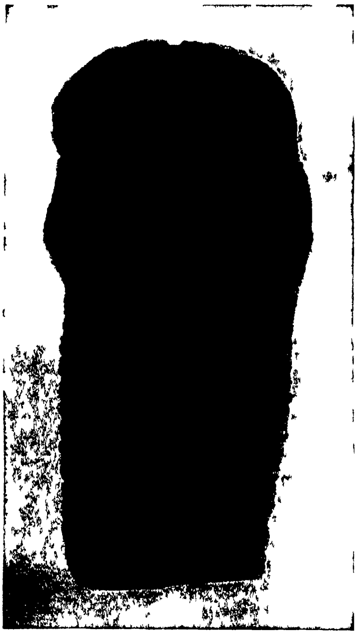

FIG. 216. Scolex of *T. saginata*, showing suckers and absence of hooklets. × 20.

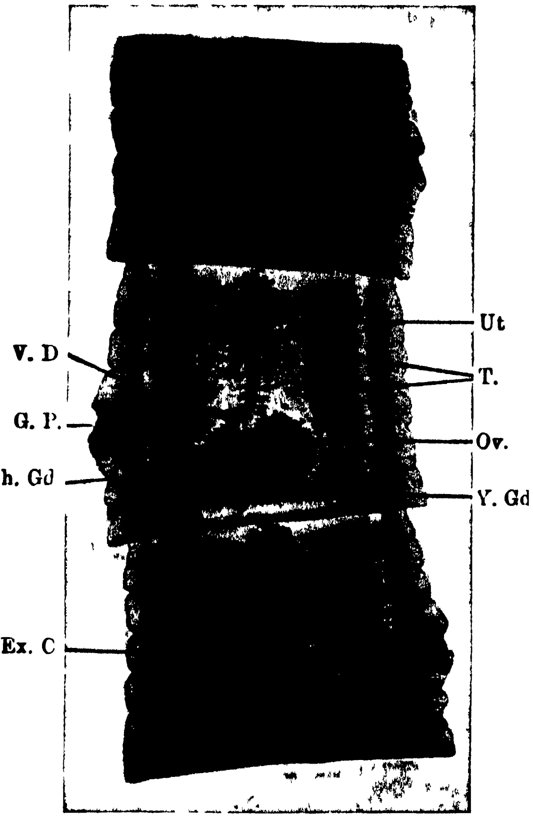

FIG. 217. Immature proglottides of *T. saginata*. Ut., uterus ; T., testes , Ov., ovaries ; Y. Gd., yolk-gland , Sh. Gd., shell-gland , G. P., genital pore ; V. D., vas deferens, immediately beneath which lies the oviduct ; Ex. C., excretory or water-vascular canal. Transverse canals joining the lateral longitudinal canals at posterior part of each segment. Note alternation of genital pores in successive segments. × 8.

The larval bladder-worm stage—cysticercus bovis—is passed in the ox, the small ellipsoidal cysts measuring from 7·5 to 9 mm. in length by 5·5 mm. in breadth. The cysticerci are usually not numerous, and are found especially in the adipose tissue around muscles and in the heart. They do not infest man.

The adult worm occurs in Britain and especially in Eastern Europe, also in Asia, Africa, and some parts of South America. It is very common in Abyssinia and in certain districts of India. The worm is usually attached high up in the small intestine, burying its head among the villi. It can be detached only with difficulty; and, because of this, and on account of its greater muscularity and more active movements, it gives rise to greater irritation than does *T. solium.* The segments migrate out through the anus independently of defæcation, as well as being passed during the act.

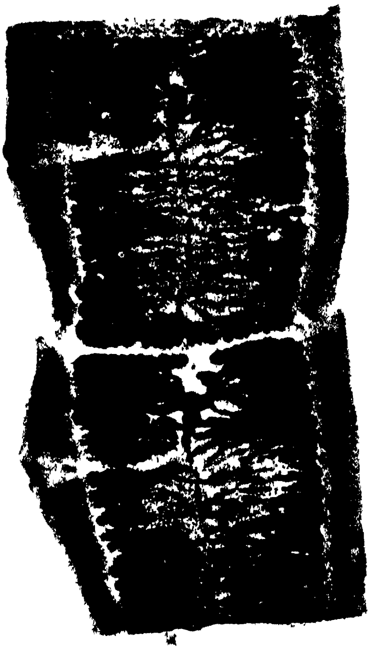

FIG. 218. Mature proglottis of *T. saginata*, showing uterus. × 6.

Pathological Effects of T. solium and T. saginata. The cysticerci in the case of *T. solium*, when situated in the brain, may cause epilepsy and other serious results (pp. 396–7 and 1151); and in the eye they may lead to loss of sight; but in the muscles and elsewhere, they produce merely pain and mechanical effects. The adult worms, living in man's intestine, may excite various symptoms of gastro-intestinal irritation—pain, vomiting and diarrhœa —and also various nervous symptoms. With both tapeworms, there are no resultant lesions demonstrable in the intestines or other organs, and the effects are due mainly to toxic products, the presence of which in extracts of the worm has been demonstrated experimentally.

Diagnosis. Examination of the fæces may show segments, but rarely free ova. Examination of the blood reveals an eosinophilia from 10 to 30 per cent.

ECHINOCOCCUS GRANULOSUS. [1] (Syn. *Tænia echinococcus*, *T. nana*, *Echinococcifer echinococcus*). This parasite is one of great importance, the presence of its immature stage in man constituting the serious disease known as **Hydatids.**

The adult is a small tapeworm, varying from 2·5 to 6 mm. in length. It inhabits the intestine of the dog, in which it is very common and often present in large numbers. It is also found in the fox, wolf and jackal, but has never been found in man. The scolex, which is like a miniature of that of *T. solium* in appearance, is usually about $\frac{1}{3}$ mm. in breadth, and is armed with four suckers and numerous hooklets measuring from 30 to 45 μ in length, usually thirty or forty in number and arranged in a double circle around the rostellum. The whole worm consists of the scolex and three or four segments, the last of which alone is mature, and may exceed the rest of the worm in size (Figs. 219 and 220). The uterus consists of a central trunk with lateral protuberances ; and the genital aperture is lateral. The ovum is thin-shelled, the enclosed embryonal envelope being also thin, spherical, and radially-striated.

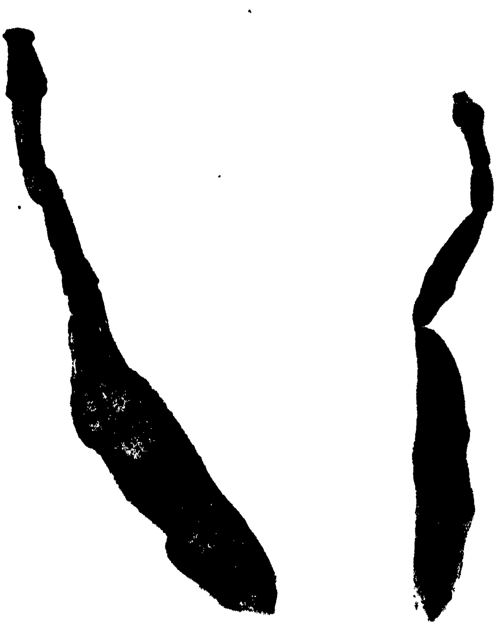

FIG. 219. *Echinococcus granulosus.*
(A) Incomplete parasite, consisting of head with hooklets and suckers, neck and two segments. × 30.
(B) Complete parasite, showing scolex and three segments—the last one mature. × 12.

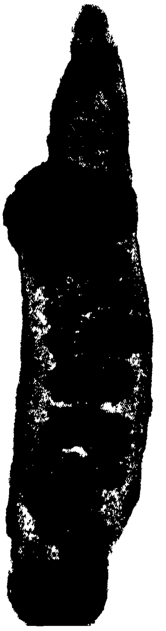

FIG. 220. *E. granulosus.* Mature terminal segment. The uterus is filled with ova. × 30.

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[1] For full details and references *see* H. K. Dew, "Hydatid Disease" (1928), Sydney.

It measures 30 to 36 μ in diameter. The oncospheres are discharged in or from the terminal segment, and may be ingested by man in contaminated drinking water, in dust, or by using imperfectly cleansed dishes from which dogs have been allowed to feed. Infestation may also occur from the kissing or caressing of pet-dogs. The embryonal envelope is dissolved off in the alimentary canal, and the liberated oncosphere or six-hookletted embryo then makes its way to the tissues—most commonly the liver, peritoneum, lungs, or pleura—in which it settles down and passes its cystic stage. It may also, however, be found in the spleen, heart and pericardium, brain, spinal cord, kidneys, muscles, subcutaneous tissue, the eye or elsewhere. In some of these positions, especially in the peritoneum, the bladder-like cysts may form large masses; and in whatever position they are found they usually give rise to serious results. This cysticercus-stage may be found, not only in man, but in oxen, sheep and pigs. The main outer or mother-cyst may, in man, attain the size of a child's head; but in cattle it does not usually exceed that of an orange.

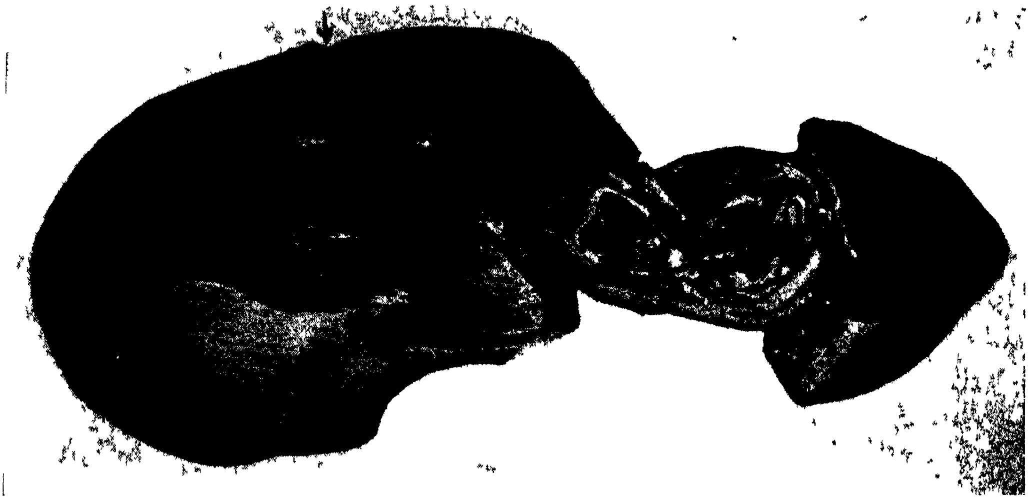

FIG. 221. *Echinococcus infestation* in a girl aged 13½ years. The liver and spleen cut across in horizontal section, showing an old hydatid-cyst lying between and adherent to the liver and spleen. This contains daughter-cysts. In the right lobe of the liver, immediately beneath the small operation-scar (marked with arrow), is seen the remains of an old hydatid cyst operated upon four and a half years previously (from a section of which Fig. 222 was made. *See also* Fig. 745, p. 1154). (Drs. Worster-Drought and Carnegie Dickson's case, W.E.H.)

Structure and Development of the Hydatid-cyst. These have already been outlined on pp. 393–4, but a more detailed account of them is needful. The following structures may be distinguished (Fig. 222, p. 402):—

i. **An outer covering of fibrous tissue,** derived by proliferation of the connective tissue of the organ or other structure in which the parasite is growing. In some situations, the development of this "capsule" may be slight, or even absent.

ii. **The ectocyst**—the true cyst-wall or hydatid-membrane—is composed *of a stratified elastic cuticle*, which in turn encloses within it the more delicate endocyst or germinal layer. The ectocyst is opaque, whitish in colour, opalescent, and in appearance bears some resemblance to boiled onion-scales. It may be stripped off in delicate layers, the laminæ tending to curl inwards. Microscopically, it shows fine concentric lamination, each lamina exhibiting a delicate cross-striation. In chemical composition, the material of which it is composed resembles chitin.

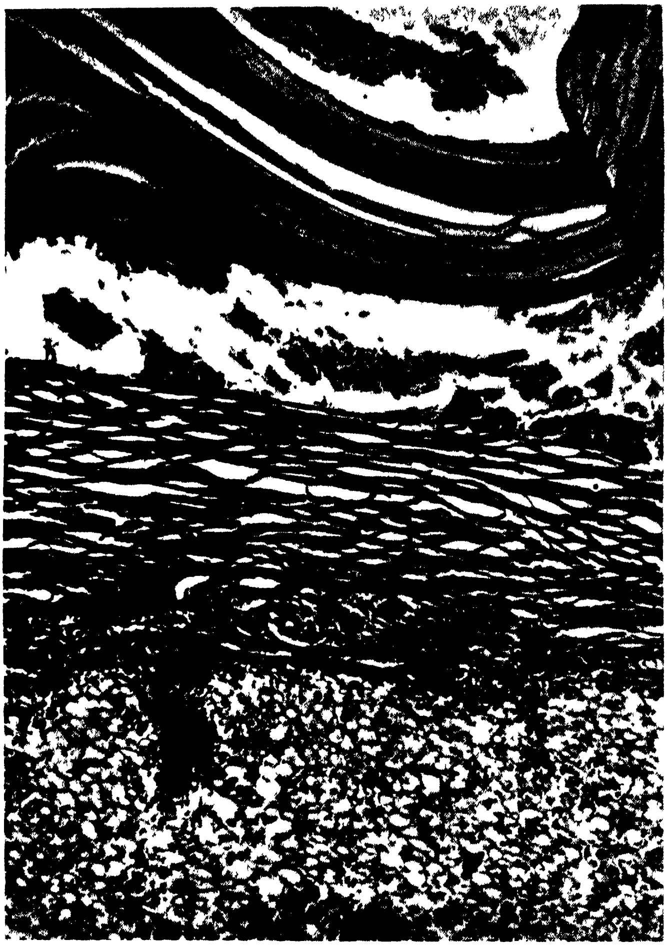

FIG. 222. *Echinococcus-infestation*. Low-power view of a section of the wall of the *hydatid-cyst* shown in the preceding Fig. 221. From above downwards are seen: the degenerated *contents* of the cyst: the thin *endocyst* (with no brood-capsules in it), lining the *laminated ectocyst*: between which and the *fibrous-tissue covering* derived from the surrounding liver-tissue is an artificial space due to retraction during fixation. The lowermost part of the section consists of much degenerated fatty *liver-tissue*. Mallory's connective-tissue stain. × 100.

iii. **Endocyst.** This consists of a cellular germinal layer, which contains calcareous bodies and glycogen. From the endocyst are developed bud-like projections or brood-capsules, each about the size of a pin's head, which become hollow, and within each of which a varying number of scolices develops. Several "generations" of endogenous cysts may be formed from the germinal layer, the "mother-cyst" coming to contain several "daughter-cysts," in the interior of which there may develop "granddaughter-" and even a further generation of cysts before the development of the brood-capsules in their interior.

The brood-capsules possess a thin cuticular layer internally, and a cellular layer on their outer surface. Scolex-formation occurs by budding from the wall of the brood-capsule, the head of each scolex being usually invaginated so that the ring of hooklets appears to be inside its body (Fig. 223). Ten, fifteen or twenty scolices may be formed within each brood-capsule, of which there may be many thousands present within the larger cysts. The base of the young scolex, by which it is attached to the interior of the brood-capsule, becomes constricted, and forms a delicate pedicle for the scolex, which has now become a somewhat globular or slightly ovoid body, in the interior of which are the hooklets and suckers. In this form it remains until it is ingested by the final host, in whose alimentary canal the scolex becomes evaginated (Fig. 224), attaches itself to the mucous membrane of the intestine, and develops into the adult worm by the usual process of budding.

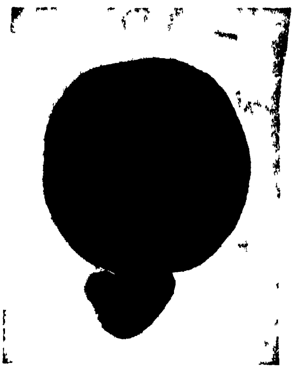

FIG. 223. Hydatid scolex under slightly higher power to show hooklets. The head is still in the inverted position. Note pedicle at lower part. × 200.

Dévé (1926) has shown experimentally that the scolices are capable of swelling and becoming transformed into hydatid-cysts. This may explain the occurrence of numerous secondary cysts, *e.g.*, in the abdomen, following rupture of the primary cyst, say, of the liver.

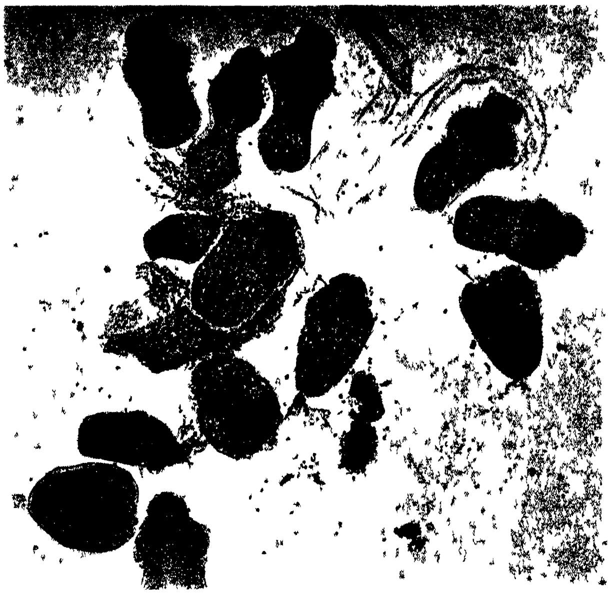

FIG. 224. Ruptured brood-capsules of *Echinococcus granulosus* with numerous scolices, most of which have become everted; the others are still inverted or invaginated, so that the hooklets appear within the scolex. × 75.

The endogenous hydatid-cysts are filled with a clear, limpid, watery fluid of low specific gravity—usually 1004–6, or a little more. This **hydatid-fluid** contains almost no albuminous material (unless inflammation has occurred). About half the total amount of solid constituents consists of sodium chloride ; whilst traces of other salts, as well as of dextrose, cholesterol, leucine, tyrosine, succinic acid, and some toxic substance are also found. The fluid possesses certain immunological properties of importance in the serum-diagnosis of the condition. If mixed with the serum of an infested patient, it gives a precipitin-reaction (p. 132), which, however, is not absolutely specific, as it may also be given with some normal sera. A more reliable test, according to some observers, is its use as the antigen in a complement-fixation reaction (pp. 132–3). When mixed with the patient's inactivated serum, it will deviate or adsorb fresh guineapig's complement, and so prevent hæmolysis of the sensitised red corpuscles used as the indicator. **The Casoni intradermal reaction** is frequently positive in hydatid-cases. A small quantity of hydatid-fluid is injected intradermally. A positive reaction, in the form of a raised wheal, may occur in from fifteen minutes to twelve hours.

Varieties of Cyst :—

i. In some cases, there may be only a **single large cyst,** without daughter-cysts, the brood-capsules being situated on its inner surface.

ii. "**Acephalocysts** " or **sterile cysts** resemble the above ; or daughter-cysts may be present, but remain barren, *i.e.*, do not develop brood-capsules in their interior.

iii. **Endogenous cysts,** *i.e.*, "mother-cysts," producing "daughter- " and "granddaughter-cysts," etc., by a process of endogenous or "cyst-within-cyst " formation. This method of development occurs especially in the case of man, and is rare in cattle.

iv. **Exogenous cysts** are similar to the foregoing, except for the fact that the daughter-cysts are formed externally to the parent-cyst.

All four of the above-mentioned are believed to be merely variants of the same species of the parasite, growing, it may be, under different circumstances and in different positions. Thus in man the cysts occurring in the liver commonly multiply endogenously ; whilst those in bone are often exogenous.

v. **Alveolar Cysts.** Hydatids with an alveolar arrangement of the cysts are rare in man, and are found more usually in cattle, giving rise to a sponge-like growth, which may in some cases resemble a colloid cancer in its naked-eye characters, the cut surface having a honeycomb-like appearance.

They are found most commonly in the liver. There has been much controversy as to whether these cysts arise from a different species of tapeworm. This has not been confirmed and the general opinion is that the alveolar form of hydatids is an unusual variant of the common hydatid, induced perhaps by unusual conditions present in the host. Most of the recorded cases of alveolar hydatids have occurred in Central and Eastern Europe.

Secondary Changes in, and Effects of, Hydatid-cysts. Spontaneous cure may in some instances occur. The hydatids may die and the fluid become gradually absorbed. The cyst may shrink, its contents degenerating and undergoing inspissation, but the hooklets persisting and remaining recognisable microscopically for a very long period. Such changes may possibly be produced by the entrance of bile, or by injury to the cyst-wall. Calcification may occur in the fibrous capsule and may be demonstrated radiologically.

Inflammatory changes and the formation of pus, due to the entrance of bacteria—*e.g.*, *Bact. coli*—may occur, and as a result spontaneous **evacuation** may take place. If the cyst is in the liver, such evacuation may be through the diaphragm into the pleural cavity, or into the lung if there are adhesions present, and the contents, having passed into the bronchi, may be expectorated. The cyst may **rupture** into the peritoneal cavity, and widespread growth of hydatids be thus set up there. Immediately following such rupture there may be severe shock and the appearance of an urticarial rash, indicating an allergic type of reaction (p. 135). There is usually a well-marked **eosinophilia** accompanying this.

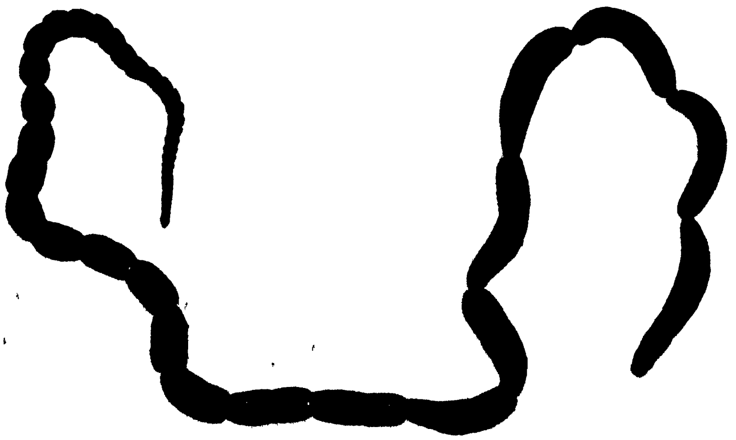

FIG. 225. *Dipylidium caninum*, illustrating the general structure of a tapeworm i.e. head or scolex, neck, immature and mature proglottides. × 4.

The **effects,** apart from such accidents as rupture or secondary bacterial infection, are due mainly to pressure on organs or vessels. In the case of hydatids of the liver or peritoneum, there may be ascites.

Distribution of Hydatid-cysts. The **liver** is the organ most commonly affected (about 50 to 75 per cent. of cases). The **lungs** come next in frequency (7 to 11 per cent.), and after them the muscles and cellular tissues, kidneys, brain, spleen and bones. The peritoneum is not infrequently involved, usually secondarily to rupture of a cyst in an organ, especially the liver.

The less important tapeworms *Dipylidium* and *Hymenolepis* need only be briefly mentioned.

DIPYLIDIUM CANINUM (Syn. *Tænia canina, T. cucumerina, D. cucumerinum*). This tapeworm is a common intestinal parasite of dogs and cats, but it is found occasionally in the human subject, especially in young children who play with these animals. The worm measures usually from 15 to 35 cm. in length and 1·5 to 3 mm. in breadth.

The head has four suckers and a hookletted club-shaped rostellum ; and the mature segments, which resemble cucumber- or melon-seeds in appearance, are 6 or 7 mm. long and 2 or 3 mm. broad, and are usually of a somewhat reddish colour. Each segment contains a single centrally-placed, reticulated uterus, whilst the other sexual organs are arranged in two similar sets, situated one on either side of the uterus, with two genital pores opening one on each lateral border, hence the generic name, *Dipylidium*. The larval cysticercoid form has its habitat in the dog-louse (*Trichodectes canis*), the dog-flea (*Ctenocephalus canis*), and in the common flea (*Pulex irritans*).

HYMENOLEPIS NANA. Though rare in Northern and Central Europe, this small tapeworm is common in Southern Europe, and has been reported in many other countries, including Japan, both Americas, the Philippines, and Russia. It varies from 10 to 45 mm. in length, and 0·5 to 0·7 mm. in breadth, and possesses a rostellum with a single circlet of some 25 to 30 hooklets. The segments are broad in proportion to their length. Many of these worms may be present in individual cases, and may give rise to serious disturbance of the health of their hosts—mostly children. Other members of this group are *H. diminuta*, parasitic usually in rats and mice, the cysticercoid larva developing in the rat-flea : and *H. lanceolata* of various birds.

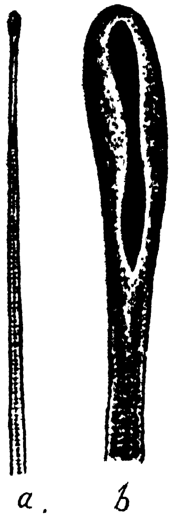

FIG. 226. *Diphyllobothrium latum*.
a. Scolex, neck and commencement of strobila (natural size).
b. Anterior extremity of the same magnified.

FIG. 227. Mature proglottides of *Diphyllobothrium latum*, showing central rosette-shaped uterus. × 8.

DIPHYLLOBOTHRIUM LATUM (Syn. *Dibothriocephalus latus*, *Tænia lata*, *Bothriocephalus latus*, *Dibothrium latum*). The broad tapeworm may attain a length of from 2 to 9 metres or more. It is greyish-yellow in colour. The head, which is minute, is elongated and flattened at the sides, or almond-shaped, with deep lateral longitudinal suctorial grooves (Fig. 226), from which the parasite derives its name.[1] It has no hooklets

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[1] βοθρίον, *bothrion*, a small trench, here the *groove* on each side of the head.

or rostellum. The neck is extremely delicate. The proglottides may number 3,000 or 4,000, or more. Towards the middle of the worm each segment measures about 4 or 5 mm. in longitudinal and 10 to 12 mm. in transverse diameter. Towards the posterior end they become narrower and more elongated, the terminal segments being almost square in outline, and containing little but the dilated uterus, which is centrally placed and consists of numerous transversely directed convolutions which, in the ripe segments, give it the rosette-shape so characteristic of this worm (Fig. 227). The sexual opening is situated on the flat ventral surface of each segment, just anterior to its centre.

The ova, unlike those of *T. solium* and *T. saginata*, do not undergo full embryonic development while still in the uterus. They retain their thin, brownish, operculated shells after they have been discharged and evacuated along with the intestinal contents. If carried to water, a free-swimming oncosphere with a ciliated embryonal envelope is hatched after an interval of several weeks. In the water it is ingested by a small copepod crustacean (usually *Cyclops*) in which it is transformed into a procercoid larva. The crustacean with its contained larvæ is in turn eaten by fish (pike, perch, etc.) in which further development into an elongated scolex, 1 to 2 cm. long, takes place. In the flesh of the fish it is transferred to the alimentary canal of its final host, *e.g.*, man, dog, cat, etc.; and if not already killed by efficient cooking it rapidly develops into the adult worm, its habitat being the small intestine, where it may be single or multiple, sometimes in considerable numbers, and not infrequently in company with *Tænia solium*. It is found most commonly in Central and Eastern Europe (the inhabitants of Finland show a very high incidence of infestation), and in Asia, especially Turkestan and Japan. In Ireland it occurs along the Shannon river.

It has been introduced into the Great Lakes, both of the United States and Canada, probably by Finnish immigrants. First recognised in Lake Superior, it has since been demonstrated generally throughout these waters. Clinically, however, in the United States, examples of infestation are discovered more often in Jewish children than in any other group. This is due apparently to their sampling the uncooked fish-mixture in connection with the preparation of *gefüllte Fisch*.

In the majority of cases, the symptoms produced in man are not very serious, but in certain instances, probably owing to the secretion of some toxin, or to poisons produced by the disease or death and decomposition of the worm itself, it may lead to the production of a profound anæmia often macrocytic in type (pp. 665–6). A similar severe type of anæmia was produced experimentally in dogs by Tallqvist with a hæmolytic, lipoid-like substance extracted from *D. latum*. Recovery from the anæmia, often rapid, usually takes place after the expulsion of the worm. The diagnosis of infestation is made by the examination of the fæces for ova and segments, the latter usually remaining united in large pieces.

NEMATHELMINTHES OR ROUND-WORMS

Of this large group of worms, only a few are of importance in man. These belong to the *Nematodes*, of which there are many Sub-orders and Families :—

NEMATODES [1], ROUND-WORMS OR THREAD-WORMS

The **Nematodes** are elongated, cylindrical, filiform, or slightly spindle-shaped worms. They are non-segmented, and are covered by a cuticle, which may show transverse striation. Beneath this layer lies the cutis and dermo-muscular tube, within which is the body-cavity containing the intestinal canal, etc. The oral aperture opens into the mouth-cavity, which is continued as the œsophagus, the posterior part of the latter usually showing a bulb-like dilatation, behind which, in some species, there is a glandular "stomach," followed by the mid- and hind-gut, the latter being, as a rule, short. They usually taper towards the head or anterior extremity, where the mouth, which may often show certain characteristic peculiarities in structure, is situated. The sexes are in nearly all cases separate, the male being generally smaller than—usually about half the length of—the female. The posterior extremity may be tapering or rounded, and is generally straight in the case of the female; whilst in the male it is usually curved, and may show peculiar modifications such as the development of a bursal or wing-like expansion, or it may be bilobed.

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[1] Nematode, like a νῆμα, *nēma*, or thread.

Development. Fertilisation of the ova occurs within the uterus. The female is usually oviparous, but is sometimes ovo-viviparous, or in a few cases viviparous. The embryos are minute filiform worm-like bodies, which generally lie coiled up within the ova. In some cases these embryos, apart from their smaller size, closely resemble the parent-worm. In other instances they at first possess certain characters which they eventually lose by a process of metamorphosis.

These miniature nematodes may reach the alimentary canal of their next host while still contained within the egg; or they may hatch in the open and live in mud or water or elsewhere before entering the body of the final host. In other important instances, *e.g.*, in the Filariæ, the immature forms are present in the blood of the definitive host and do not undergo further development until they are transferred to the body of an intermediate host—often a blood-sucking insect—*e.g.*, a mosquito in the case of *Wuchereria bancrofti* (Syn. *Filaria sanguinis hominis*), in which they then undergo metamorphosis.

In certain exceptional cases, *e.g.*, in *Trichinella*, the embryos do not leave the body of the host which harbours the parent-worms, but utilise it also as intermediate host, encysting in the muscles or elsewhere, until they are transferred, along with the tissue in which they are embedded, to the alimentary canal of the second host, which may or may not be of the same species as the first. In their new host they then undergo further development and become mature.

Some nematodes are parasitic only during their adult stage, the larval form being free-living in water or in mud (*e.g.*, ankylostoma).

FAMILY 1. ASCARIDÆ

In the members of this family, the mouth is provided with three lip-like papillæ, one dorsal and two latero-ventral. The œsophagus possesses a bulb-like expansion. The tail of the male is curved, and the genital aperture is furnished with two spicules and numerous small papillæ. The female genital opening is situated, as a rule, anterior to the middle of the worm, which is oviparous. No intermediate host is required, development being direct.

ASCARIS LUMBRICOIDES[1] **or COMMON ROUND-WORM.** This parasite somewhat resembles the common earth-worm in appearance, having a long, cylindrical body, tapering towards both ends. The female measures from 20 to 25, or even as much as 40 cm. in length, and about 5 mm. in diameter: the length of the male being from 15 to 25 cm., and its breadth about 3 mm. In colour they are reddish or greyish-yellow. In their general characters and structure these worms conform to the family description given above, the tail of the female being straight, and that of the male strongly hooked or curved ventrally.

The ova (Fig. 201, *f*, p. 384) measure 50 to 70 μ in length by 40 to 50 μ in breadth. They possess a transparent shell, surrounded externally by a thick albuminous envelope, which has a rough knobbed, or mammillated appearance externally, and which stains yellowish-brown with the bile of the fæces, in which they may occur in enormous numbers: they are very resistant, and survive

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[1] *Ascaris*, from *σκαρίζειν* or *σκαίρειν*, *skarizein* or *skairein*, to frisk or dance (like a calf), hence here to wriggle. *Lumbricoides*, like a *Lumbricus* or earth-worm.

desiccation and cold for a prolonged period. In favourable circumstances, they remain alive for as long as five years or more. The ova, when passed, are usually unsegmented, the embryo taking several weeks to develop.

When ingested, the embryo or larva emerges from the egg in the small intestine, penetrates the wall and reaches the liver, mainly by the vascular system, thence it travels to the heart and then to the lungs. Here the larvæ grow and, in experimental animals (rats and mice), they may produce a fatal pneumonia if there is a heavy infestation. It has also been shown experimentally in man that the immature worms reach the lungs and may appear in the sputum. Having entered the alveoli, they then travel up the bronchi and trachea and reach the œsophagus and so pass down to the intestines, where they develop into the adults. This cycle is similar to what obtains in the case of *Ankylostoma* (*q.v.*).

In the rat and mouse the larvæ are evacuated as such and do not develop into adults in these animals.

Man becomes infested from soil, or by foodstuffs contaminated by ova or embryos, *e.g.*, passed by rats or mice. Insanitary conditions thus favour infestation.

The parasite inhabits especially the upper and middle parts of the small intestine, but it may occasionally find its way into the stomach. Usually only a few worms are present, but in rare instances enormous numbers may be found. Its geographical distribution is practically universal. It is one of the commonest parasites of man, both in adults and in children, and it occurs also in monkeys, dogs and pigs.

The **pathological effects** of the presence of the worm in the intestine vary greatly. They may be slight, or there may be produced severe nervous symptoms, but whether these are toxic or merely reflex in nature is disputed. The worms may invade and cause obstruction of the common bile-duct or pancreatic duct, and may penetrate a considerable distance and be found in the liver, gall-bladder, or interior of the pancreas ; and, in exceptional circumstances, they may bore through the intestinal wall, and give rise to peritonitis or to localised abscess-formation.

Occasionally the worm migrates up the œsophagus and appears in the mouth or nose, and has been known to reach the frontal or other accessory nasal sinuses, or pass along the Eustachian tube to the middle ear. In women, they have occasionally been found in the bladder. Cases of suffocation due to their impaction in the glottis have been described, and they may even pass down into the trachea and bronchi. In some febrile and toxic diseases, and also sometimes just before the death of the host, the worms migrate from the body.

ENTEROBIUS VERMICULARIS (Syn. *Oxyuris vermicularis*). **The THREAD-WORM, SEAT-WORM or PIN-WORM.** These are small white round-worms, the female measuring some 10 mm. in length by about 0·5 mm. in breadth, and the male usually 3 to 5 mm. by 0·16 to 0·2 mm. The posterior end of the male is truncated and markedly curved, and is furnished with a single spicule and six anal papillæ, while that of the female is longer and tapers to a sharp point.

The ova (Fig. 201, *h*, p. 384 and Fig. 228, below) are minute, thin-shelled bodies, measuring about 50 μ in length and 16 to 24 μ in breadth, and are slightly flattened on one side. They usually contain a small coiled-up embryo, which is, as a rule, not liberated from the shell until it reaches the human duodenum, though the larvæ have also been found in the nose. Direct infestation occurs through the mouth, to which the ova may be conveyed by the fingers, *e.g.*, infected finger-nails, or by fruit or vegetables or dust, which have been contaminated with the ova. Development is complete in three or four weeks. The ova survive indefinitely if kept dry, but are said to perish after prolonged immersion in water. An intermediate host is not required.

These parasites are common in children. The habitat of the young and maturing worm is the small intestine, cæcum and appendix, and perhaps the proximal part of the colon. The impregnated females, when mature, descend into the rectum, where they produce their ova, they themselves passing out with the fæces. They also migrate out *per anum*, especially when the patient is warm in bed, and cause great itching and irritation. They may enter the vulva, vagina or bladder, giving rise to much irritation. Their presence in the intestine produces little or no obvious pathological effects, but sometimes, and especially in weakly children, they cause reflex nervous symptoms, fits and enuresis. They have been found in association with appendicitis (Fig. 230), typhlitis, and entero-colitis, and have been discovered in the interior of nodule-like swellings in or beneath the intestinal mucosa and in anal and rectal fistulæ. Severe eczema is in some cases produced around the anus and neighbouring parts.

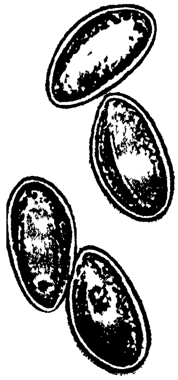
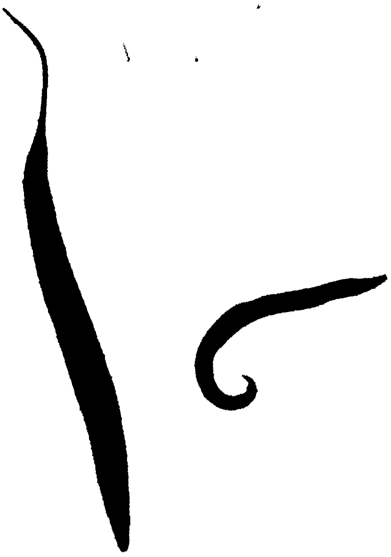


FIG. 228. Ova of *Enterobius vermicularis*. × 300



Female. Male.

FIG. 229. *Enterobius vermicularis*, showing relative size of female and male, and characteristic curved tail of the latter. × 10

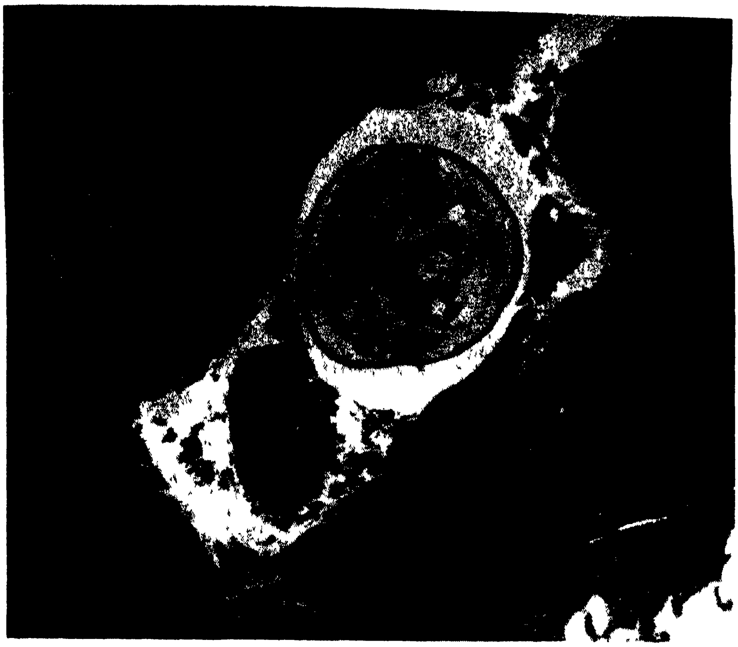


FIG. 230. Transverse section of vermiform appendix removed for suspected appendicitis. In its lumen is a cross-section of a female *Enterobius vermicularis* containing many ova. × 80.

ANKYLOSTOMIDÆ

This is a large and important family, the members of which are characterised by the possession of six oral papillæ; and the mouth may also be armed with chitinous teeth. The posterior extremity of the male is furnished with an umbrella-like copulatory expansion and one or two spicules.

Human ankylostomiasis may, for all practical purposes, be regarded as due to the two species, *Ankylostoma duodenale* and *Necator americanus*. Both of these are sometimes found in the same individual.

ANKYLOSTOMA[1] **DUODENALE or HOOK-WORM** (Syn. *Dochmius ankylostomum*, *Strongylus duodenalis*, *Dochmius duodenalis*, etc., and, in America, *Uncinaria duodenalis*).

This important parasite is, in its adult form, the cause of **Egyptian chlorosis, miners' disease, miners' anæmia, brickmakers' anæmia or tunnel-disease**; whilst its embryonic form causes skin-eruptions known variously as **ground-itch, water-itch, coolie-itch,** etc. It is distributed widely throughout most tropical and subtropical countries, more especially in Egypt, India and Ceylon, the Far East, Brazil, and many other parts of America, including the Southern United States. It is found also in Southern Europe, having been first discovered by Dubini in Italy in 1843. It attacked many of the workers digging the St. Gothard Tunnel (1871–1881), and is endemic in certain parts of Germany, Austria, Hungary and other parts of Central Europe; and in

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[1] Variously spelled *Ankylostoma*, *Ancylostoma*, *Anchylostoma* or *Agchylostoma* (the *g* being a mistaken transcription of the Greek letter γ, which, when, as here, it precedes the letter κ, or occurs before the letters ξ or χ or another γ, should be given the value of our *n*, as in "angel"—*not* "aggel"!—from ἄγγελος). The Greek words from which the word *Ankylostoma* is derived are ς, crooked, and στόμα, mouth.

Cornwall, among the tin-miners, it is by no means uncommon. During the Great War of 1914–18, ankylostomiasis was very prevalent among the troops in Egypt, especially in the Egyptian Labour Corps, and amongst Indian troops in Palestine, East Africa and Mesopotamia, and amongst the native African soldiery.

The worm is cylindrical in shape, the head being tapering and the posterior extremity more truncated. The length of the female is about 12 mm. and its breadth 0·6 mm. The anus is subterminal and the posterior extremity is furnished with a small spine. The vulvar orifice is situated ventrally and is slightly behind the junction of the middle and posterior third of the body. The male is about 9 mm. in length and 0·4 to 0·5 mm. in diameter; and its posterior extremity is furnished with a characteristic umbrella-like copulatory bursa, supported by eleven chitinous rays or ribs, and possessing three wing-like processes. The genital orifice, situated in the concavity of the bursa, is equipped with two long, slender spicules.

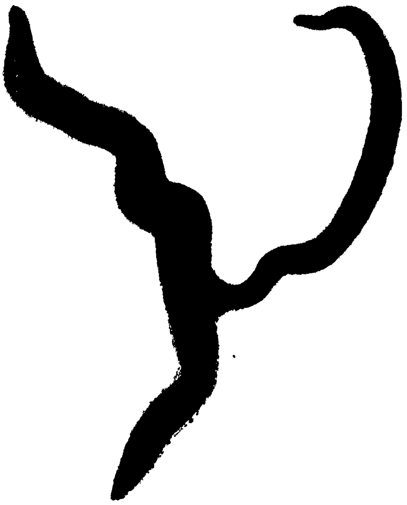

FIG. 231. *Ankylostoma duodenale*, showing relative sizes of male and female. Both show the characteristic hooked anterior extremity. The male is smaller than the female, and its posterior extremity shows the umbrella-like copulatory bursal expansion applied to the vaginal opening of the female. × 7.

The worm is pinkish-white in colour when alive, or brownish-red if gorged with blood, but is greyish-white when dead. The head in both sexes is slanting or bent (hence the generic name meaning "squint-mouth"), the opening of the mouth being directed dorsally. The oral cavity is armed with four hook-like teeth and two conical papillæ. The muscular œsophagus is strongly developed and, by means of this structure, the worm draws in the intestinal mucous membrane of its host and fixes it by means of the powerful buccal armature above described. Having attached itself to the mucous membrane, the worm by quick sucking-movements ingests blood which it rapidly passes through its alimentary canal into the intestinal lumen of its host. The ova are ovoid in shape, measuring 55 to 60 μ in length by 35 to 40 μ in breadth. They possess a thin transparent shell which does not stain with bile, and through which the segmenting embryo may be seen (Fig. 201, *i*, p. 384, and Fig. 232 below). A varying degree of development occurs as the ovum passes down the intestine, segmentation into four divisions being usually seen at the stage when the ovum is expelled from the bowel in the fæces.

The habitat of the worm is especially the upper part of the jejunum, and to a less degree the duodenum. In exceptional circumstances it may be found in the stomach, or in the ileum or large intestine. The worm is believed to shift from place to place on the mucous membrane, and loss of blood may also occur from the abandoned sites.

Life-History. The segmenting ovum (Fig. 201, *i*, p. 384 : and Fig. 232 below), after leaving the body of the definitive host in the fæces, rapidly develops under suitable conditions of moisture and temperature (*e.g.*, 25° to 30° C.), development being retarded if too much water is present, and also if there is an insufficient supply of oxygen : or if too much sunlight is present. In a day or two a rod-shaped larva, measuring 0.25 mm. in length and 14 to 17 μ in diameter, is hatched out (Figs. 232 and 233). The larvæ, so produced, are actively motile and can swim in water or wriggle up a moist surface. They grow rapidly in moist earth or mud, moulting their cuticle twice, and attaining a length of about 0·5 mm. and a diameter of 24 μ. Further growth now ceases, and a more sluggish stage supervenes, during which the larva can remain alive in water or moist earth for several months. The larvæ are now infective and, as has been demonstrated by Looss, actively make their way through the skin, if brought in contact with the latter in water or mud. They bore their way, sometimes by way of the hair-follicles, into the skin and subcutaneous tissue, where they may wander about, causing an

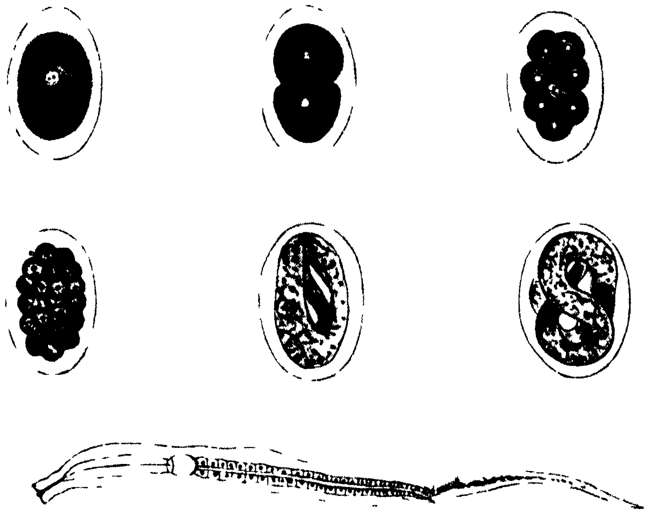

FIG. 232. Ova of *Ankylostoma duodenale*, showing segmentation and development of the embryo within the clear transparent shell. The hatched-out rod-shaped larva is shown below. × 300.

eczema-like skin-eruption ("ground-itch," "coolie-itch," etc.). The larvæ may then enter the lymphatic channels and pass by them into the thoracic duct and thus into the venous circulation; or in other instances they may enter a small subcutaneous vein and so reach the venous circulation directly. They are then carried through the right side of the heart to the lungs, in which they burrow into the air-vesicles and later into the bronchi, where they cast their envelope for the third time. They next make their way up the bronchi and trachea, either in the mucous secretion in the lumen, or along or in the substance of the mucous membrane. On reaching the glottis they are swallowed or make their way down the œsophagus to the stomach and intestine, where the final moult occurs. This remarkable journey is believed to take from seven to ten days to complete. The worm, having now become sexually mature and having attained its adult form, attaches itself to the mucous membrane of the intestine. Eggs may appear in the fæces seven to ten weeks after the occurrence of infestation.

Ankylostomiasis or Uncinariasis. Because of the wide distribution of the hook-worm throughout many parts of the world, as detailed above, the important and serious disease produced by it is equally widespread, causing much disability in the inhabitants of affected areas. Its prevention is one of the major activities of medical officers in tropical and subtropical regions, and this is now possible from a full knowledge of the life-history and factors necessary for the development of the parasite, especially in its larval stage.

The infestation may sometimes exist—especially if only a few worms are present—without producing much injury to health, the infested individuals acting as carriers; but even slight degrees of ankylostomiasis usually cause some degree of debility and loss of weight, and tend to aggravate any other diseases from which the host may suffer, and conversely, the minute injuries produced by the parasites, both by the adults in the intestine and the larvæ in the skin, favour infection by bacteria.

The pathological effects are due, in the first instance, to the penetration of the skin (" coolie-itch "), as mentioned under development of ova. As they pass through the lungs, the larvæ may set up a bronchitis. The adults in the intestine cause local abdominal pain and discomfort. Owing to their action on the mucosa and the associated loss of blood, an anæmia develops and may become extreme. Œdema of the face and ankles, and ascites, may supervene, and enlargement of the liver, accompanied by jaundice and irregular and intermittent fever. The spleen is not enlarged. Retinal hæmorrhages, believed to be toxic in origin, are of frequent occurrence. Examination of the blood shows a hypochromic microcytic anæmia. The red corpuscles are reduced in number, perhaps, in serious cases, to a million or less per c.mm.; whilst the hæmoglobin is diminished both in percentage and amount per corpuscle, the colour-index in the latter case being reduced frequently to less than a third of the normal figure. Normoblasts are often present, megaloblasts less commonly, and the red corpuscles usually show considerable poikilocytosis, and sometimes polychromatophilia. In recent infestations, the leucocytes are increased, *e.g.*, up to 56,000 (Boycott and Haldane). The eosinophils especially are, as in the majority of cases of helminthiasis, increased in number, and, in this disease, usually constitute about 8 per cent. or more of the total leucocytes, the highest percentage of eosinophils, recorded by Boycott and Haldane, being 66 per cent. in two cases of recent infestation in which the total leucocyte-counts were respectively 56,000 and 44,000 per c.mm. The eosinophilia usually becomes less pronounced as the disease becomes more chronic. Certain severe cases may show no increase of eosinophils. In cases which have not progressed too far, rapid recovery may follow the expulsion of the parasites.

On post-mortem examination, in addition to the changes due to the anæmia —*e.g.*, pallor and œdema of the tissues, serous effusions, fatty degeneration of the organs, and perhaps the accumulation of iron-pigment in the liver—evidence of the nature of the disease may be seen in the small intestine itself. The worms may be found still adhering to the mucous membrane in considerable numbers; or—and especially if the post-mortem is made some time after death—they may have relaxed their hold and be found in the lumen of the bowel. The positions recently occupied by the worms on the mucous membrane may be seen as numerous little punctiform hæmorrhagic spots, each with a minute wound in its centre, whilst little points of pigmentation mark the older sites. Acute or chronic intestinal catarrh is often present, and, locally, the affected part may be covered with slightly blood-stained mucus, though any pronounced degree of melæna is uncommon.

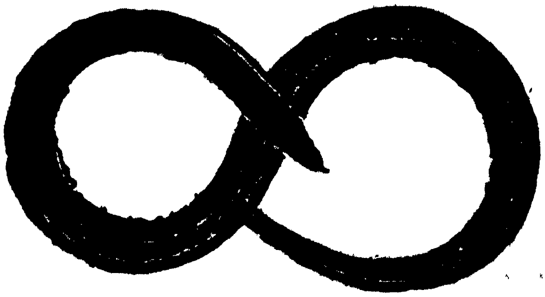

FIG. 233. *Ankylostoma duodenale* embryo. Hatched out from ovum in damp petri-dish in incubator for four days at 37° C. × 300.

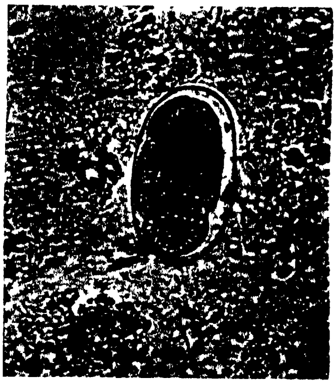

FIG. 234. Ovum of *Ankylostoma duodenale* in fæces, showing thin transparent shell and segmentation of embryo. × 300.

Various other species of *Ankylostoma* (*e.g.*, *A. caninum*), infesting certain of the lower animals, are described and have been utilised in working out the life-history of the Genus.

NECATOR AMERICANUS (Syn. *Ankylostoma americanum*, *Necator africanus*, *Uncinaria americana*). The American variety of **hook-worm** or **tunnel-worm** closely resembles *Ankylostoma duodenale* both in general structure and with regard to the symptoms which it produces. It may, however, be distinguished from the latter by its smaller size, by the more strongly-marked dorsiflexion of the head, and by the absence of the four ventral hook-like teeth, instead of which it possesses a semilunar chitinous cutting-plate on each side, meeting in the middle line in front. The dorsal margin of the mouth is furnished with two slightly developed chitinous plates. The buccal cavity is small, and has, deeply placed within it, two pairs of lateral lancet-like teeth. There are also certain minor differences found in the copulatory bursa of the male, and the ova are somewhat larger than those of *A. duodenale,* measuring 65 to 75 μ in length and 35 to 40 μ in breadth, and are more pointed at the poles. The life-history of this worm is similar to that of *A. duodenale.*

This worm has been found only in man and the gorilla. It occurs in North and South America and widely throughout the African Continent, and it has also been described as occurring in India, Ceylon, Assam and Burma, and in Queensland.

TRICHURIS TRICHIURA (Syn. *Trichocephalus trichiuris, Ascaris trichiura, Trichocephalus hominis, T. dispar*). *T. trichiura,* the **common whipworm,** is a frequent parasite in man. The thin thread-like cephalic extremity, constituting about the anterior three-fifths of its entire length, resembles the lash of a whip, the " handle " being formed by the stouter posterior two-fifths of the worm. The female measures 45 to 50 mm. in length, the thick posterior part being straight, whilst in the male, which measures 40 to 45 mm. in length, the posterior part is curled up into a spiral. The male possesses a single long spicule, with a sleeve-like, retractile sheath. The ova (Fig. 201, *g*, p. 384 and Fig. 236) measure usually 50 to 55 μ in length, and about 25 μ in breadth. They are ovoid or somewhat barrel-shaped, with a thick brownish shell, showing at each end a characteristic clear knob-like plug resembling a " stopper." They are resistant both to cold and drying, and are usually unsegmented when passed, incubation taking place in water or mud. No intermediate host is necessary. On reaching the human stomach, the shell is digested away, and the embryo thus liberated becomes mature in four or five weeks.

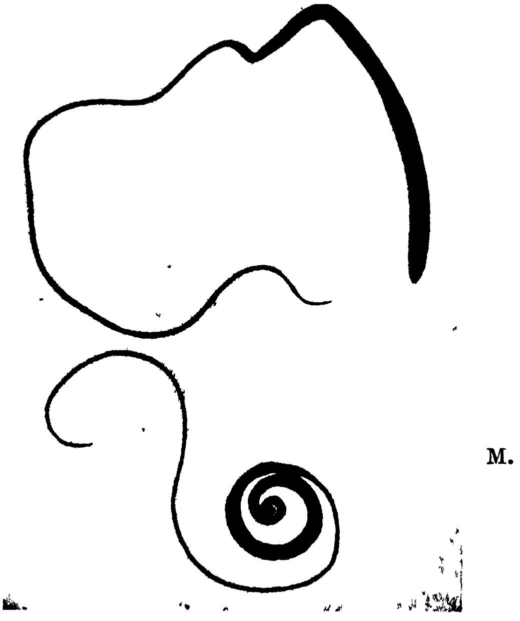

FIG. 235. *Trichuris trichiura.* F. female. M. Male. × 2½.

Its special habitat is the cæcum and commencement of the large intestine, to the inner surface of which it is said to attach itself by transfixing a fold of the mucous membrane with its thin anterior extremity, or by burrowing its pointed head into a gland. It

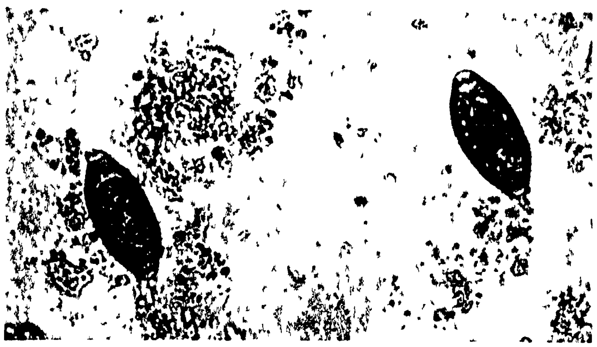

FIG. 236. Ova of *Trichuris trichiura* in fæces. × 300.

occasionally finds its way into the interior of the vermiform appendix. As a general rule, however, its presence gives rise to no serious pathological results, though it may occasionally be associated with a severe anæmia (p. 665).

T. trichiura is found in some monkeys and in lemurs as well as in man.

TRICHINELLA SPIRALIS (Syn. *Trichina spiralis*). This worm in its immature or larval state is the cause of **trichiniasis** (**trichinosis** or **trichinelliasis**) of muscle in man, in the rat and mouse, the pig, dog, cat and other animals. Infestation of the human subject is brought about by eating trichinosed and imperfectly cooked pork : and especially the dangerous and reprehensible habit of **eating raw uncooked pork-sausages** or **sausage-meat** spread as a sandwich, a practice not uncommon amongst working-women and to which many cases in the recent epidemics in Wolverhampton, London, Birmingham and elsewhere in this country during the present war have been traced. The adult worm inhabits the alimentary canal, more especially the small intestine, of the same hosts. The male is about 1.4 to 1.6 mm. long and 0.04 mm. broad. After impregnation, the female increases considerably in size—3 to 4 mm. in length and 0.06 mm. in diameter—chiefly on account of the dilatation of the ovarian tube, which acts also as a uterus. This organ contains enormous numbers of ova in which segmentation and the rapid development of the little worm-like embryos may be observed to have occurred. The egg-shell disappears and the embryos are free within the mother, which in the five to seven weeks of her career may give birth to many thousands of living embryos. During this period, she has made her way through the mucous membrane by active boring until she comes to lie in a lymphatic space. There she liberates her young into the lymph-stream, by which they enter the circulation and are carried to all parts of the body, the diameter of the newly-born larva (6 μ) being somewhat less than that of a red blood-corpuscle, and its length 90 to 100 μ. The larvæ are motile, but, in reaching the striped muscles in which they finally aggregate, active migration plays a minor part. In the main, they appear to be carried passively by the lymph- and blood-streams. They may be found in all the voluntary muscles, but are seen especially in those of the abdomen and thorax, diaphragm, tongue and pharynx. They do not encyst in the myocardium. In the muscles, they are usually aggregated towards the surface and the tendinous ends, perhaps because of the relatively slighter degree of movement in these parts. Enormous numbers of larvæ reach the muscles, each larva entering one of the muscle-fibres. These become enlarged and lose their transverse striation, the nuclei at the same time undergoing proliferation. The little worm-like embryos have by this time enlarged somewhat, and traces of an alimentary canal appear. They now are in a quiescent stage and become spirally coiled up within cyst-like capsules, each of which arises from the transformation of a damaged muscle-fibre and the surrounding tissues, aided possibly by the presence of some substance secreted by the larva itself. This process of encystment in the muscles is completed in about eighteen days after the primary intestinal infestation, and the next host becomes infested by ingesting the flesh of the animal in which the parasites are encysted. The fully-formed cyst is typically lemon-shaped, with somewhat pointed ends, its long axis lying in the same direction as that of the muscle-fibres which are pushed aside to make room for it. The wall is composed of clear refractile homogeneous material and shows a double contour. Some slight proliferation of connective tissue may occur around the cyst. After several months, the wall of the cyst begins to undergo calcification, the process commencing generally at the poles and spreading towards the equator of the cyst. The larva, if uncoiled, measures about a millimetre in length and in its encysted condition may remain alive and capable of further development for many years— in man, over thirty years in some cases, it is said. Sometimes, however, the larvæ in the cysts die off and become calcified. When the muscle infested with living *Trichinella* larvæ is ingested by the next host, the calcified cyst-wall is dissolved by the gastric juice and the liberated larva develops in a few days into the adult worm, which then reaches its habitat in the duodenum and jejunum. Copulation occurs as early as two days after their ingestion. The males then die and the impregnated females enlarge and bore their way into the mucous membrane, as already described. In the course of their combined migration and transportation throughout the body, larvæ, in considerable numbers, frequently reach the cerebrospinal fluid, so that diagnosis is sometimes made by lumbar puncture and examination of the fluid (p. 1155).

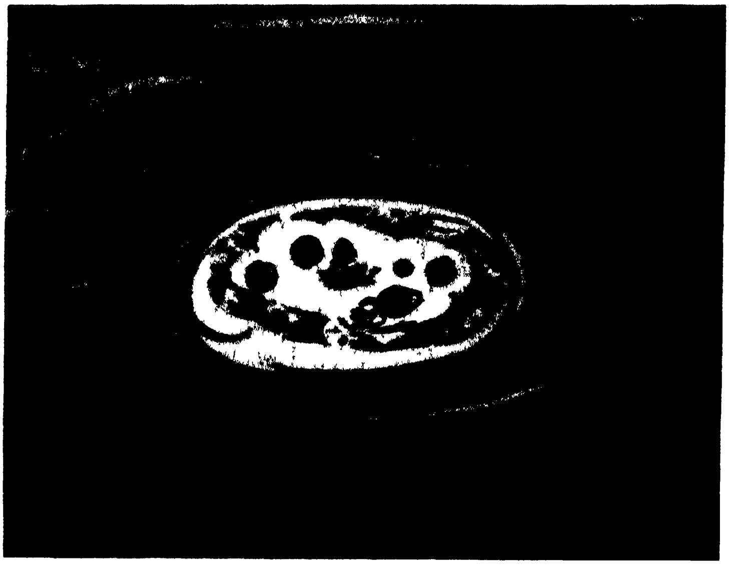

FIG. 237. Trichinosed muscle. *Trichinella* embryo encysted in human muscle. (*See also* Fig. 746, p. 1155.) × 125.

Pathological Effects in Man. **Œdema of the eyelids,** unaccompanied by any albuminuria, is often the earliest characteristic sign of the disease ; and, during the period of invasion of the muscles by the larvæ, there may be severe pain and myositis, the muscles becoming swollen and hard ; and, later, there is usually extensive œdema of the body. Severe cases have been mistaken for typhoid or rheumatic fever, and are characterised by fever, headache, nausea, vomiting, abdominal pains and diarrhœa, pain on using the muscles of mastication, speech, respiration, etc., and intense dyspnœa and often accompanying cough. Convalescence may supervene about the fifth or sixth week ; or death may occur from interference with the action of the respiratory muscles, or from pneumonia or some other secondary complication. Symptoms resembling those of meningitis or other forms of involvement of the central nervous system are of frequent occurrence in some epidemics (p. 1155). The most common cause of death is **myocardial failure** due to trichinous myocarditis. This **myocarditis** is due probably to the invasion of the muscle by the larvæ, which, however, perhaps on account of the constant movement of the heart, do not encyst in this position, but are destroyed at an early stage of their development. The myocarditis may be severe and widespread, and, in the affected heart-muscle, the areas of inflammatory infiltration contain many eosinophils. The occurrence of larvæ in the interstitial tissue makes it probable that the myocarditis is due to their immediate presence in the heart and not to a circulating toxin. In the blood, there may be a moderate leucocytosis, of which the **eosinophils may constitute 30 to 50 per cent., or more.** The degree of the **eosinophilia** varies in different cases, and is most pronounced during the period following the primary intestinal infestation, until encapsulation of the larvæ in the muscle is complete. The occurrence of the eosinophilia is of value in differential diagnosis ; and a positive biopsy-examination of the infested muscle will establish the nature of the disease. An intradermal skin-sensitivity test (Bachman) and serum-precipitin test become of some value at about the second and fourth weeks respectively.

The disease occurs usually in epidemics, especially in countries such as Germany where uncooked or partially cooked pork ("*schinken roh*") is eaten extensively ; even the pickling of pork does not kill the parasite. In a series of some 500 general post-mortems in America (University of Buffalo Pathological Institute), examined specially for the presence of trichiniasis, 5·34 per cent. of the bodies were found to be infected, half of the positive findings being in mental cases, in which, however, the trichiniasis was stated not to be the direct cause of death. The incidence disclosed in a series of autopsies will depend upon the method of search employed. The routine examination of microscopical sections detects only the occasional case. A much larger number will be found by teasing and crushing a sample of muscle. In various pathological institutes in America, an incidence of from 15 to 20 per cent. has been revealed by the method of employing peptic digestion of 50 grammes of diaphragmatic muscle from each cadaver. Infestations of a degree insufficient to be diagnosed clinically must be relatively common. In Britain, trichiniasis in man was, until the serious outbreaks of the disease during the present war, only rarely encountered.

DRACUNCULUS MEDINENSIS (Syn. *Filaria dracunculus*, *F. medinensis*, *Guinea-worm*, *Medina-worm*, *Dragonneau*). This parasite, the cause of **Dracontiasis,** is found in Arabia, Persia, Egypt, Tropical Africa, along both its East and the West Coasts, India, and in many other localities, and its geographical distribution is said to have some relation to the presence of rivers. It produces subcutaneous swellings, followed in some cases by abscess-formation, especially in the lower limbs.

The **female** is 50 to 100 cm. in length, and 0·5 to 1·7 mm. in diameter. It is white or yellowish-white in colour, with faint transverse striation, and is uniformly cylindrical, except for a slight degree of tapering towards the cephalic end. Below the level of the œsophagus the alimentary canal is atrophied, and the anus is absent. The greater part of the body-cavity is occupied by the enormous uterus, which runs almost the entire length of the worm and is crowded with larvæ, the female being viviparous.

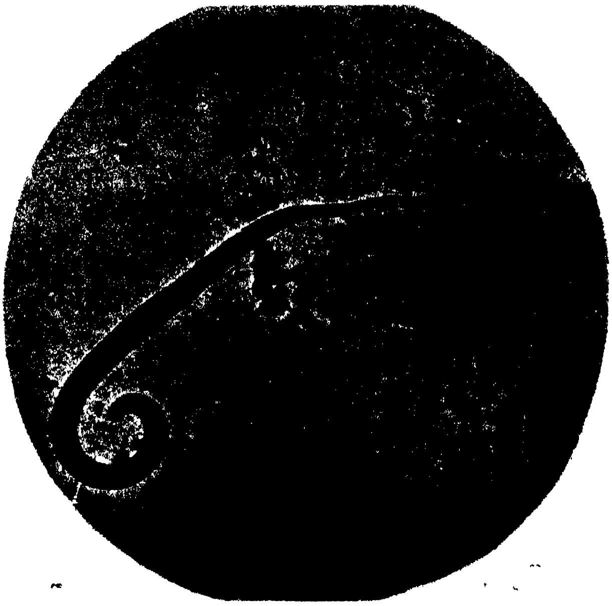

FIG. 238. Larval form of *Dracunculus medinensis*, showing coiled-up " body " and tapering " tail." × 200.

The **male** is much smaller, measuring from 20 to 40 mm. in length. It is rarely found in the tissues.

The female, when she reaches sexual maturity, gradually works her way through the tissues of the host, generally in a downward direction, till she reaches the surface, usually on the lower limb in the neighbourhood of the ankle, less frequently on the thighs or genitals, occasionally on the arm, and, very rarely, on the head. Her head pierces through the true skin, but not through the cuticle, a minute clear blister filled with fluid being formed. This then ruptures, a little ulcer being produced, in the centre of which is a small pore through which the female periodically discharges her larvæ in enormous numbers, contained in droplets of opalescent fluid. Sometimes during parturition a considerable length of the delicate transparent uterine tube " prolapses " through the opening. This process may be stimulated artificially by douching the skin of the part with cold water, this being apparently the natural stimulus required, as the larvæ after their discharge pass the next stage of their existence in the body of a minute fresh-water crustacean—a copepod belonging to the Genus *Cyclops* (*e.g.*, *C. coronatus*, *C. quadricornis*, and others). The larvæ measure about 0·6 mm. in length by

17 or 18 μ in diameter, have a slender tapering tail and are coiled up within the uterus of the parent-worm. When passed into water, these little larvæ unroll themselves and become actively motile. They swim about until they are ingested by the *Cyclops*, and in the body-cavity of this small crustacean the larvæ undergo moulting on two occasions. They are at first actively motile, but after three weeks or a month they enter upon a quiescent stage, the cuticle and the tail being cast off. Whilst in this condition and while still within the *Cyclops* they may be ingested in drinking water by man, or they may possibly escape from the body of the *Cyclops* and gain entrance to the human body by the mouth. After monkeys have been fed on the infested *Cyclops*, the adult worm may develop in them. The hydrochloric acid of the gastric juice kills the *Cyclops*, the larvæ resume their motility, and it is supposed that they bore their way through the wall of the alimentary canal and, as they mature, slowly migrate through the tissues, especially to the retroperitoneal region. This process may occupy a period of from eight or nine up to fifteen months or more.

Pathological Effects. During the migration of the maturing worm through the tissues, the patient may be quite unaware of its presence, though there may be attacks of general or localised urticaria. On its appearance at the surface, however, the little blister and ulcer are formed and may cause great irritation, especially if the parent-worm is injured during an injudicious attempt at extraction or in any other way. Very serious inflammatory changes with perhaps abscess-formation may supervene upon the liberation from the injured worm of larvæ into the tissues, and amputation may be rendered necessary. After the female worm has emptied her uterus by the periodic discharge of the larvæ, a proceeding which usually occupies a fortnight or more, she tends to leave the body of her host. In some cases she may succeed in doing so spontaneously, or the process may be aided by gentle traction. If the parasite during its period of migration fails to reach the surface of the body, it may die and undergo complete calcification, rendering its identification by X-rays possible.

FILARIASIS

Under the term "**Filariasis**" is included a group of diseases caused by worms belonging to various Genera of the Sub-family of *Filariinæ*.

There are many members of this group and the life-history of many of them is still unknown. Some have been recognised only in the **adult** form, some only in the **larval** form, and classification and relationships are, therefore, still in many cases provisional only.

The adult worms vary in length in different species, but all are filiform and live in connective tissues, and, in some species, particularly in lymphatics; and they frequently move from place to place. The larval forms—known as **Microfilariæ**—are frequently found within blood-vessels.

Transmission is by various species of biting-insects in which the embryos develop to the larval stage.

With regard to the causal parasites, only the more important species need be mentioned. First in importance is :—

WUCHERERIA BANCROFTI (Syn. *Filaria bancrofti*). **Larva—MICROFILARIA NOCTURNA** (Syn. *Filaria nocturna*, *Filaria* or *Microfilaria sanguinis hominis*, *F.* or *M. wuchereri*). The adult worm of this species inhabits the lymphatic system, and is found in lymphatic vessels—especially about the pelvis and groins—in the thoracic duct, or in lymphatic swellings. The lymph-nodes most frequently affected are the inguinal, femoral, iliac, lumbar and mesenteric, and bronchial. The adult worms are found also occasionally in the testis, epididymis, spermatic cord, tunica vaginalis, breast, and in abscesses elsewhere. The female is a thin filiform worm, whitish or opalescent in colour, measuring 80 to 100 mm. or more in length by about 0·3 mm. in diameter. It is uniformly cylindrical, with no very distinctive characters. Both extremities are more or less blunt and rounded, the head somewhat resembling the end of a bougie. The male may be distinguished by its spirally twisted tail, equipped with two unequal spicules, and its smaller size—about 25 to 30 mm. in length by 0·1 mm. in diameter. These worms may live for many years in their human host.

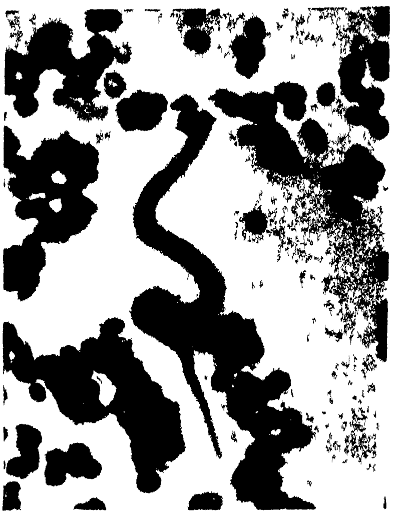

FIG. 239 *Microfilaria nocturna* (the larval form of *Wuchereria bancrofti*) in the blood. The larva is enclosed in the chorional sheath, which is seen projecting at the ends of the worm. × 300.

The male and female are usually found coiled up in a mass together. They are generally few in number, but as many as eighteen have been found in one swelling. The two long uterine tubes of the female, which is ovo-viviparous, are crowded with ova and larvæ in all stages of development. The ova containing these coiled-up larvæ (or embryos) measure 40 to 50 μ in length and about 25 to 35 μ (*i.e.*, some three, four or five times the diameter of a red blood-corpuscle) in breadth. In the later stages of development, the larvæ cause the shell or vitelline membrane to elongate so as to form a delicate sheath or investing-membrane round them. This they retain after birth. Under exceptional circumstances, such as injury or bacterial infection of the tissues, the female may give birth to ova instead of elongated larvæ, a point of considerable importance, as the greater breadth of the ova may cause blocking of the lymphatics; whereas the larvæ, which are about 0·2 to 0·3 mm. long, have a breadth of only about 8 μ—*i.e.*, are seldom very much broader than the diameter of a red corpuscle, and can therefore easily pass through lymphatics and capillaries.

When examined alive in fresh blood, the larva is seen to be a little eel-like parasite, which is transparent and colourless, with a rounded anterior and a finely-tapering posterior extremity. It is enclosed within the clear colourless transparent sheath, the origin of which has been explained above.

This chorional sheath is usually about one-third longer than the larva, which may be seen wriggling actively and also elongating and retracting itself within it. By these movements it stirs up the corpuscles around it, but it does not appear to travel with any rapidity from one place to another. The larvæ are covered by a cuticle and subcuticular dermo-muscular layer, the former of which shows fine transverse striation. Beneath this lie numerous closely-packed cells, the nuclei of which show up well in stained specimens. At various points, clear spots or areas may be seen in the granular central mass, which represent rudimentary organs and which are of some importance in identifying and distinguishing the different species of *Microfilariæ*. At the thicker anterior end of the larva there is a delicate six-lipped prepuce-like retractile structure, which may be seen alternately covering and uncovering the head, from which an extremely fine sharply-pointed spine or fang may be observed protruding at intervals.

Periodicity and Location of the Larvæ. From the body of the mother-worm the larvæ pass directly into the lymph-stream by which they are carried into the blood. They are not distributed uniformly, but aggregate especially in the capillaries of the internal organs, more particularly those of the lungs. They are found in the peripheral circulation only at night, or rather during the hours of sleep, as they may be found during the day if the patient sleeps then. In ordinary circumstances, these *Microfilariæ* begin to appear in the peripheral blood about five or six in the evening, and increase in numbers until midnight. They then gradually diminish and, by seven or eight in the morning, have usually almost but not absolutely disappeared. During the day they seem to lodge in the viscera, more especially in the lungs and larger blood-vessels, and to a lesser extent in the capillaries of kidney, liver, spleen and brain. In a considerable proportion, over 60 per cent. it is said, of persons suffering from adult-filarial infections, larvæ may not be found in the blood, either because the female ceases to produce them, possibly because no male worm is present to fertilise her, or because of her death, or for some other as yet unexplained reason.

This part of the life-cycle may continue indefinitely in man, sometimes for many years, the *Microfilariæ* never becoming mature worms, a process which can occur only on transference to a suitable intermediate host, a mosquito. Individual *Microfilariæ* can survive in the blood of man for at least seventy days.

Metamorphosis in the Mosquito. The farther development of these larvæ occurs in the females of certain Genera and Species of **Mosquito,** more especially, but not by any means exclusively, those belonging to the Genus *Culex*. This mosquito, on biting an infested person while the larvæ are in the peripheral circulation, may ingest some of these along with the blood it draws. In the stomach of the mosquito, the ingested blood becomes viscid and fixes or holds the sheath, so that the *Microfilaria*, by means of the finely-pointed spine at its anterior end, can rupture and emerge from it one or two hours after ingestion by the insect. The free, actively-motile larva can now travel from one locality to another. By means of its cephalic boring-apparatus it penetrates through the stomach-wall and bores its way to and lodges in the large thoracic or wing-muscles of the mosquito. In this position, which it reaches within a few hours—usually about twenty-four—after ingestion, it becomes quiescent and undergoes a process of maturation and metamorphosis which occupies from one to three weeks. During this period it becomes shorter and thicker (110 μ by 13 μ), forming a pupa- or cocoon-like body, sausage-shaped, with a short spike-like tail. It develops a mouth surrounded by four lip-like structures, and also an alimentary canal, and either three or four papillæ on the tail. It next undergoes a process of moulting, and increases rapidly in size and activity, attaining a length of about 1·5 mm. and a breadth of 0·025 mm. (25 μ). It then leaves the thoracic muscles, bores its way forward through the prothorax and neck, passes into the head of the insect and comes to lie near the base of the proboscis—not in the salivary gland or duct as in the case of the malarial parasite. Later, it passes into the proboscis, where it lies free among the stilettes, waiting until the mosquito bites a suitable host. The parasites have been observed to pass out in pairs—probably male and female together. Man, the final host, is thus re-inoculated when bitten by an infested mosquito, and the male and female worms pass into the lymphatics, where they become mature, and in turn give rise to further generations of larval embryos. Female worms are usually much more numerous than males.

Filariasis due to *Wuchereria bancrofti* occurs in practically all tropical countries, *e.g.*, India, China, Indo-China, Japan, Australia, Polynesia, Egypt, Algeria, Tunis, Zanzibar, Madagascar, the Southern States of America, South America and elsewhere.

Pathological Effects of Filarial Infection. These may be extremely varied and for a full description of them reference should be made to text-books on Tropical Medicine. They can be epitomised as follows :—

Large numbers of persons may be infested by both parent- and larval worms with little or no evident pathological results. If the blood be examined, there is usually found to be present in it a varying degree of eosinophilia, which may show cyclical variations corresponding to the periodicity of the *Microfilariæ* in the peripheral circulation. The healthy fully-formed larva appears to be practically harmless ; and in the same way the healthy parent-worms may give rise to little trouble. In other cases, however, the parent-worms, which lie coiled up in the lymphatic trunks or in the thoracic duct, may cause mechanical obstruction of these. They are probably more liable to do so if they themselves are diseased, and they may then produce serious results. Thus around the diseased or dead worms, great inflammatory thickening of the lymphatic trunks in which they lie, and also of the surrounding tissues, may occur. This can bring about narrowing or thrombosis of the lymphatic vessels, leading to varicosity of the distal vessels, or to lymphatic œdema in the corresponding drainage-area or, it may be, to a combination of both these conditions. Occasionally, abscess-formation occurs around the diseased or dead worms. Such abscesses are found, not only in or around the usual habitats of the parasite, but also in various muscles, and they often contain fragments of dead *Filariæ*.

Because of this blockage of the larger lymphatic channels and thoracic duct, the lymph and chyle cannot pass into the blood by the usual route, and a compensatory collateral circulation is slowly established. A backward flow occurs through the lymphatic vessels of the pelvis, perineum, groins and external genitals, by which the chyle from the intestines and the lymph from the lower half of the body is passed on through the lymphatics of the anterior abdominal wall and back. It can then be carried by the larger afferent channels which reach the thoracic duct above the level of the obstruction. From the increase of pressure in these various groups of lymphatics, great varicosity may be produced in them. In this way may arise the so-called **elephantoid** conditions, a group of diseases of which the following are the most important :—

i. **Lymphatic varices,** *e.g.*, of the thoracic duct, pelvic and other lymphatics. These may occur also in lymph-nodes, which may become much distended with chylous lymph. Clinically, this condition may show as varicosity of the inguinal lymph-nodes, but, on post-mortem examination, these are found to be merely the superficial, and therefore visible, representatives of a much more extensive series of enlarged nodes, those of the pelvis being usually most affected.

ii. **Lymphatic ulcers** are produced by inflammation or injury of superficial lymphatic varices, and may be characterised by extensive lymphorrhœa.

iii. **Lymph-Scrotum,** or enlargement of the scrotum from the distension of its lymphatics, is also brought about by the establishment of this collateral anastomosis, and may be accompanied by complications such as orchitis with enlargement of the testis, chylocele, etc. In the same way, the labia, etc., occasionally become affected in the female.

iv. By the rupture of some of the distended lymphatic channels, escape of the regurgitating chyle and lymph takes place in different localities :—

> **Chyluria and Lymphuria**—from the rupture of renal, vesical or other lymphatics, allowing escape into the urine. The milky urine is sometimes also blood-tinted.
>
> **Chylous Diarrhœa**—an analogous condition in the intestine.
>
> **Chylocele**—the escape of chylous fluid into the cavity of the tunica vaginalis testis. Adult *Filariæ*, sometimes calcified, may be found in the thickened wall of the sac, and *Microfilariæ* occasionally in the fluid contents.
>
> **Chylous Ascites**—its escape into the peritoneal cavity (p. 759).

v. **Elephantiasis Arabum.** In this condition there is enormous enlargement of certain parts of the body due to hypertrophy of the subcutaneous tissues and accumulation of lymph in them. The skin of the part is thickened and indurated.

The cause of the condition is lymphatic blockage and associated inflammatory changes. It is preceded and accompanied by recurrent attacks of lymphangitis in the affected part, due to the products which are set free by the death and disintegration of the adult worm. The attacks of lymphangitis are allergic in character and the end-result is great thickening, obliteration in certain areas, and dilatation and varicosity of the lymph-vessels, with resulting general lymph-stasis. It is possible, as suggested by Manson, that the female worm may at times set free ova instead of live embryos, and that these ova, being broader than embryos, may cause extensive blocking of the smaller lymph-vessels.

In this connection it is interesting to note that Drinker,[1] in America, has been successful in reproducing in animals a condition resembling elephantiasis by the repeated injection of crystalline silica with 2·5 per cent. quinine hydrochloride in the neighbourhood of lymphatic trunks—resulting in their permanent obstruction, with excessive fibrosis of the tissues and thickening of the skin.

Sites of Elephantiasis. In some 90 or 95 per cent. of the cases it is the lower limbs, either one or both, that are affected (Fig. 240). The scrotum (Fig. 241) is frequently attacked, reaching enormous dimensions, *e.g.*, 10, 20,

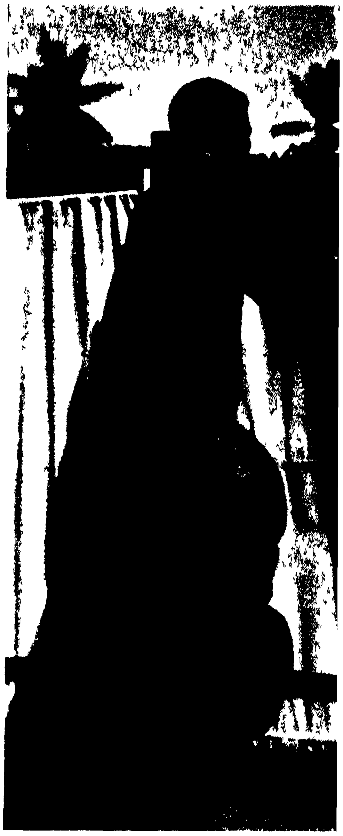

FIG. 240. *Elephantiasis of lower limb.* From Samoa.

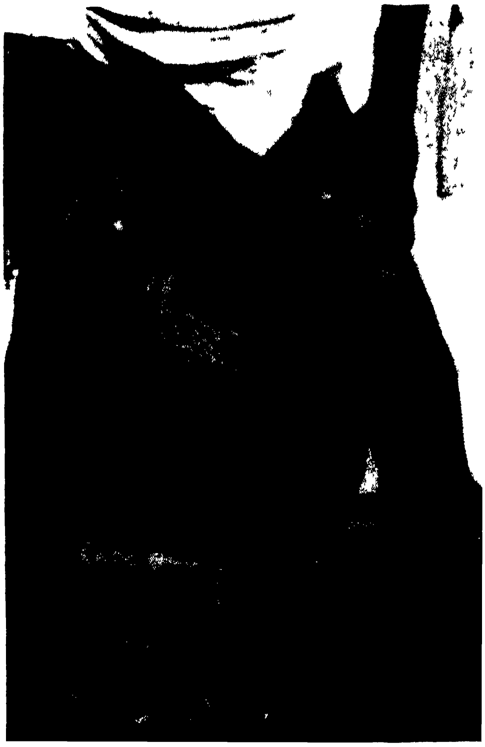

FIG. 241. *Elephantiasis of scrotum.* The penis has been buried in the enormously enlarged scrotum. The lower limbs are not affected. From India. (By courtesy of J. R. Cameron, F.R.C.S.E.)

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[1] *Bulletin of the New York Academy of Medicine*, 1938, **14**, 231 (quoted in leading article on "The Lymphatic System in Health and Disease," *Brit. Med. Jour.*, 1940, ii, 788).

40, or 50 lb., and, in some cases, very much more. Elephantiasis of the upper limbs is comparatively rare, and of the vulva and mammæ is still rarer. Occasionally, limited areas of skin may be involved, *e.g.*, of the groin, thigh or neck.

Elephantiasis is due most commonly to *Wuchereria bancrofti* (*Filaria bancrofti*), but it has also been found associated with *Onchocerca*, and with a little-known species, *Filaria malayi*, of which only the larval form has yet been identified.

ONCHOCERCA. There are two recognised pathogenic species of this filaria—*O. volvulus* (Syn. *Filaria volvulus*), found in Tropical Africa, Ceylon and China, and *O. cæcutiens*, found in Central America and Mexico. They are very similar in their general characters and pathogenic effects. The female is about 50 cm. long by 0·3 mm. in diameter; the male is much smaller, about 30 mm. long by 0·13 mm. in diameter. The female is viviparous, producing numbers of embryos similar in general appearance to those already described for *W. bancrofti.*

The adults live in the subcutaneous tissues and form superficial swellings, and masses of worms may be found in these with much induration around. The embryos are set free into the tissues and accumulate in the skin, producing a dermatitis. The lesions may occur on any part of the body, but in some cases, and especially in the infestation with *O. cæcutiens*, the swellings may be on the head and the *Microfilariæ* may invade the eyes, producing conjunctivitis, iritis, and finally complete blindness.

Whilst lymph-varices are not produced by these worms, occasionally a minor degree of elephantiasis results from the inflammatory reactions which they excite.

Transmission is by biting-insects, most commonly some species of the fly *Simulum;* but the tick *Ornithodorus moubata* (p. 431) has also been found to carry the embryos. Further development, similar to that of *W. bancrofti* in the mosquito, occurs in the fly or tick, and infestation is conveyed by them when the larvæ are mature and have migrated to their biting-apparatus.

LOA LOA (Syn. *Filaria loa, F. oculi, Dracunulus oculi, D. loa*). **Larva—MICROFILARIA DIURNA** (Syn. *Microfilaria loa, F. sanguinis hominis,* var. *major, F. diurna*). The male of *L. loa* measures from 25 to 35 mm. in length and 0·3 to 0·4 mm. in diameter. The female may be from about 45 to 65 mm. long, and about 0·5 broad. Both sexes are covered with small irregularly distributed chitinous protuberances, and the cuticle does not show striation. The cephalic end is blunt and the tail is tapering, that of the male being incurved. The ova, when the contained larvæ are developed, are about 50 by 25 μ in diameter; whilst the uncoiled larvæ measure about 0·25 mm. in length, and some 5 μ in diameter.

The **habitat** may be not only the eyelids, the anterior chamber of the eye and the connective tissue of the conjunctiva and other parts of the orbit, but also the connective tissue and fat beneath the skin or under the muscular aponeuroses on the extensor surfaces of the upper and lower limbs, or in the tissues of the fingers, trunk, under the tongue, pericardium, penis, and possibly in lymphatic vessels, *e.g.*, of the spermatic cord. The infestation is frequently multiple, as many as thirty worms having been found in a single case. The parasites wander about in the tissues, sometimes with considerable rapidity, as may be seen when they are present under the skin where it is thin, *e.g.*, in the eyelid, etc. They give rise to transient and shifting œdema and redness, constituting the so-called Calabar swellings. Eosinophilia, *e.g.*, of 50 per cent. or more, is usually present. The worm is apparently very long-lived, and has been known to persist for fifteen years or more.

Microfilaria diurna was believed by Manson to be the larval form of *L. loa.* As its name implies, it is found in the peripheral circulation during the day. It possesses a sheath derived from the stretched vitelline shell, and in general characters closely resembles *Microfilaria nocturna. L. loa* is found on the West Coast of Africa, especially the Congo ; and Leiper has shown that the development of the larva occurs in the salivary glands of *Chrysops*, a mango-fly.

Many other filariæ have been described, but they are of minor importance from a pathological point of view and further reference need not be made to them here.

EPI- or ECTO-PARASITES

These are parasites living usually on the surface of, or in, the skin, though some come only into casual contact with man. Their importance depends mainly on the fact that serious disease may be transmitted by their bites or excrement, *e.g.*, plague by fleas, spirochætal fever by ticks, etc. They belong to various groups of the metazoa.

LEECHES

(Phylum *Annulata*, Class or Order, *Hirudinea.*)

These are only occasional or accidental parasites of man, who may be attacked while bathing, or working in water or wet grass, etc., containing them, or by drinking such water. They may attach themselves to the mucous membrane of the pharynx, larynx, trachea, œsophagus, nose, etc. In rare instances, leeches have obtained entrance to these parts when applied medicinally. In some moist tropical regions, a species of *Hæmadipsa* (Looss) may drop from bushes or trees in considerable numbers on to its victims, including man, and suck their blood. Leeches are potential carriers of disease, as they act as hosts of trypanosomes and other parasites.

MITES AND TICKS

These are Arthropods belonging to the General Class of *Arachnoidea* and Order *Acarina.*

I. MITES

LEPTUS AUTUMNALIS. This name is applied to the larvæ of several species of mites belonging to the genus *Trombidium*, which are specially plentiful in the late summer and autumn, and are known variously as "harvest-, "autumn- or "grass-mites," "gooseberry-bugs," etc. These larvæ are minute reddish bodies about 0·25 mm. in length. They possess a long hypopharynx—the so-called "suctorial proboscis"—which they insert into the skin in order to suck the blood of their host. They give rise to great irritation, with the production of wheals, and are parasitic, not only on man, but on many other mammals. In Japan, a serious disease known as kedani, akamushi, river- or flood-fever, is due probably to a *Rickettsia*-infection following upon the bites of a *Leptus*-like mite (*Trombicula akamushi*).

SARCOPTES SCABIEI—(Syn. *Acarus scabiei*)—or **Itch-mite**[1]. The male measures 0·2 to 0·3 mm. and the female 0·35 to 0·45 mm. in length. They are more or less spheroidal in shape and pale in colour, the back and legs being covered with chitinous bristles. The larvæ possess only three pairs of legs, but in the next stage of development—the nymph—another pair appears. Both larvæ and nymphs form burrows in the epidermis. The nymphs then develop into the adult sexual forms ; the sexes pair, and the male dies off after copulation. The impregnated female undergoes certain modifications in structure, and proceeds to burrow in the epidermis, laying her eggs, usually about the rate of two per day, until some fifty ova in all are deposited at intervals in the tunnel. The ova, which are ovoid, with a long diameter of 0·15 mm., hatch in a few days, giving rise to the six-legged larvæ. Maturity is reached in eight to ten days, during which period the parasites moult three or four times, undergoing metamorphosis to nymph, pubescent adult, and adult. The females are found at the ends of the burrows. These are tunnels in the deeper part of the horny layer, and are seen as minute curved or wavy lines in the skin, a few millimetres in length, mostly between the fingers, along the ulnar border and palm of the hands, and over the wrists, elbows and knees, axillæ, breasts and genitals. Minute vesicles usually form at the points of entrance, and sometimes also at the positions occupied by the females and larvæ. Suppuration may occur in these vesicles, the surrounding skin becoming red and inflamed, from the presence both of the mites and of secondary bacterial infection due to scratching. Impetigo-like crusts may also be formed over the affected part. **Crusted scabies**—frequently termed " Norwegian itch," but found also in most other European countries, as well as in Turkey, South America and the Pacific area—is characterised especially by the formation of crusts, and has been considered by some to be due to a possibly distinct species, " *Sarcoptes scabiei-crustosæ*," derived, perhaps, from some host other than man ; but more

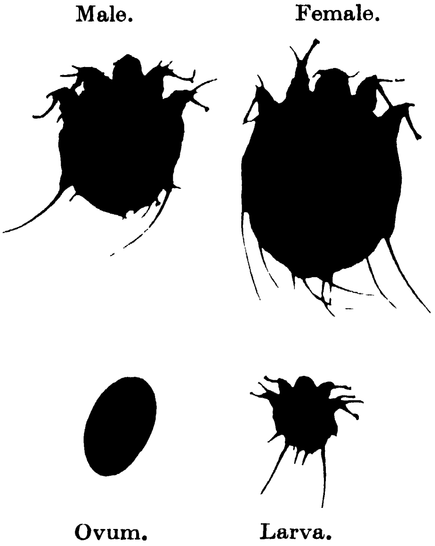

FIG. 242. *Sarcoptes scabiei* or itch-mite. × 80.

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[1] Some of the above information concerning itch-mites is taken from an article, " The Parasitology of Scabies," by Professor P. A. Buxton, London School of Hygiene and Tropical Medicine, *Brit. Med. Jour.*, 1941, ii, 397.

frequently it is due, in all probability, merely to the neglect of an ordinary "human" type of infestation.

Infestation in man is usually acquired by contact with an already infested person; or from the horse, dog or other animal, including the camel—but not, it is said, from birds, which apparently do not suffer from "mange." Epidemics have also been traced to intermediary sources such as the contamination of the leather railway-carriage straps ("strap-hangers' itch"). The mites burrow most actively when the skin is warm, *e.g.*, at night when the patient is warm in bed, and thus, at these times, producing great itchiness. The infestation can be conveyed by bed-clothes and garments that have been in contact with an infested person. No intermediate host is required, and it is not known whether the infestation can be conveyed from man to animals.

Numerous closely-allied forms of itch-mite are found in other mammals besides man, and various forms of "mange" in animals are due to such itch-mites.

Various other mites have been described as occasional **internal parasites** in man, but such infestations are uncommon. One of the authors has now investigated over a dozen such cases, in several of which[1] large numbers of mites in all stages of their development, from ova to adult, were passed in the urine. One case was that of a young woman with urinary symptoms which lasted many years in whom, on cystoscopic examination by the late Sir John Thomson-Walker, the mites, *Aleurobius* (or *Tyroglyphus*) *farinæ*, were found to inhabit especially the trigone of the bladder. In a second case, a middle-aged male, mites belonging to the family *Tarsonemidæ* were found in the urine obtained both from the bladder and from the pelves of both kidneys on ureteral catheterisation.

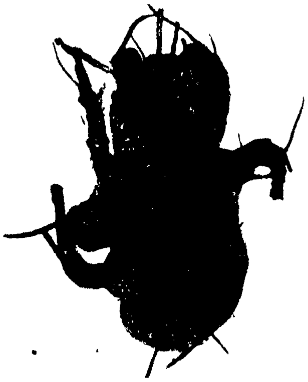

FIG. 243. *Aleurobius* (*Tyroglyphus*) *farinæ*. Adult male from human bladder. × 100.

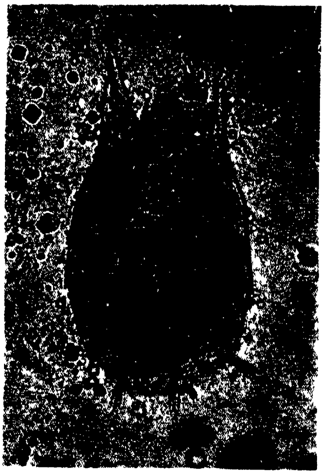

FIG. 244. *Tarsonemus* (species undetermined). Adult female from pelvis of human kidney. Structure is somewhat obscured by the oxalate crystals, etc. × 200.

DEMODEX FOLLICULORUM. This is a small, degenerate form of mite, belonging to the Family *Demodicidæ*, several varieties of which are parasitic in man, in the hair-follicles, and in the Meibomian and sebaceous glands. It is of comparatively little pathological importance. Similar parasites occur in the dog and pig.

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[1] Carnegie Dickson, "Mites as Internal Parasites of Man." Communicated at meeting of Pathological Society of Great Britain and Ireland, March 27th, 1920, and Medical Society of London, January 10th, 1921. *Journal of Tropical Medicine and Hygiene* (1921), **24**, 25.

II. TICKS (IXODIDEA)

These are of importance from the fact that, in addition to being found as epiparasites upon man and many of the lower animals and birds, they act as carriers of protozoal and bacterial diseases, and also some forms of helminthiasis.

Ticks are divided into two Families, **Argasidæ** (or **Argasinæ**) and **Ixodidæ** (or **Ixodinæ**). Members of both groups have been found to be pathogenic in man.

Ticks may live in crevices of old buildings, native huts, etc., and are often nocturnal in their wanderings, hence man may be attacked when resting in such infested dwellings. Other hosts may shelter the ticks and man be only an accidental host. The whole life-cycle can be passed on one host, or part of the cycle may be on another host or on the ground. Most ticks are long-lived and survive for several years, even without nourishment. Both adults and nymphs may bite and gorge themselves with blood. Infectivity may be transmitted through the egg to the next generation, *e.g.*, the virus of Rocky-Mountain spotted fever in *Dermacentor* (see below). The bite of the tick may pass unnoticed, no trace being left, or a puncture-mark or wheal may persist. Only a few characteristic species of ticks need be mentioned here.

ARGAS PERSICUS, found in Asia and Africa, America and Australia, transmits the *Spirochæta marchouxi* (*Sp. gallinarum*) of spirochætosis of fowls, as does also *Ornithodorus moubata.*

ORNITHODORUS MOUBATA. This tick is widely distributed in Africa, and is the carrier of the *Spirochæta duttoni* of **African Tick-Fever** (p. 373). It has also been found experimentally to harbour the microfilariæ of *Onchocerca volvulus* (p. 427) and the virus of yellow fever (p. 122).

DERMACENTOR ANDERSONI —(Syn. *D. venustus*)—the **Rocky-Mountain Tick-Fever** tick, is found especially in America. It is a parasite of cattle, horses and other large mammals, and only incidentally affects man. It conveys the infective agent (*Rickettsia*) of " Spotted Fever of the Rocky Mountains " to man. Ticks of other species may convey a closely allied fever, noted first in 1929 in Sao Paulo. In Canada and the United States this tick conveys tick-paralysis to man and sheep. The American dog-tick may by its bite cause a flaccid paralysis of the legs, and other nervous symptoms, especially in children. The disease persists until the ticks have been detected and removed, *e.g.*, from the scalp, improvement then as a rule rapidly taking place.

IXODES RICINUS. This is a ubiquitous tick and infests many animals—cattle, sheep, deer, dogs, birds, etc. It may also attach itself to man. In cattle it transmits *Piroplasma bovis*, the cause of red-water, or Texas-fever of cattle. (This protozoan may be conveyed by other ticks, *e.g.*, *Margaropus annulatus.*) In sheep it has been found to cause "tick-borne fever," a viral disease which possibly may affect man also. The tick also conveys the virus of " louping-ill " in sheep.

INSECTS

These are *Arthropoda*, breathing by means of tracheæ, and with bodies divided into three separate regions, head, thorax, and abdomen. The head, formed by the fusion of about six segments, is equipped with four pairs of appendages, antennæ, mandibles, maxillæ with their palpi, and fused second pair of maxillæ forming the labium or lower lip, each side carrying its labial palp. The ocular segment carries the eyes. The mouth-parts are developed and modified for biting, sucking, etc., according to the life-habits of the individuals. Development is usually complex, and, when hatched from the ova, the young or larvæ (maggots, caterpillars, etc.) as a rule differ greatly from the adult both in form and habit of life ; and, in order to reach the adult stage, they generally undergo metamorphosis during a quiescent period of pupation. Some possess wings, one or two pairs ; in others, these are rudimentary or have been lost ; whilst others again are wingless.

Insects are of vast importance in the economy of nature, and from man's point of view their activities are both helpful and harmful. It is with the latter that we are here concerned. The destructive activities of insects as regards crops, stores, provisions, etc., do not come into our province, except where these lead to the contamination and infection of food, etc. The *rôle* of the house-fly and all its kind, of ants, beetles, etc., in thus carrying infection and disease is now fully recognised, and typhoid, cholera, dysentery, summer-diarrhœa, tuberculosis, anthrax, tetanus, and a host of other diseases may be so conveyed. Similarly, the transmission of disease by biting-insects is a subject of extreme importance, but for full descriptions of mosquitoes, midges, and sand-flies, tsetse-flies, and other insect-carriers of disease, special text-books must be consulted, though passing reference has been made to them in this volume when dealing with such diseases and the parasites causing them (malaria, yellow fever, etc.). The danger of spread of disease by **insect-vectors** is now enhanced owing to **air-transport,** and various regulations are in force for its prevention.

We shall deal here merely with a few of the commoner and more important insect-parasites of man, some of which are also vectors of disease.

Many insects are casual or occasional epiparasites upon man. Some produce severe irritation by injecting a salivary secretion when they bite. Infection with bacteria, especially streptococci, at the site of the bite leads on occasion to serious results.

MYIASIS. The larvæ of some dipterous insects may become parasitic in man and animals. **Internal** or **Gastro-Intestinal Myiasis**—due to the presence of larvæ of the *Œstridæ* (the bot- or warble-flies), *Sarcophagidæ* (the flesh-flies, such as *Sarcophaga carnaria*, *S. magnifica*, etc.) : certain *Muscidæ*, *e.g.*, *Fannia* or *Anthomyia canicularis* (the small house-fly), *Musca domestica* (the common house-fly): *Calliphora*, *Cynomyia*, etc. (the blue-bottles), and *Lucilia*, *Pycnosoma*, etc. (the green-bottles)—is less common than **External Myiasis,** in which the skin, outer ear, pharynx, nose and its accessory sinuses, urethra and vagina may be involved. Some of the above-mentioned flies, as well as the screw-worm fly (*Chrysomyia*) and certain of its relatives occasionally lay their eggs in these positions in sleeping or debilitated persons, and, during the War of 1914–18, severe maggot-infestation of exposed wounds[1] was by no means uncommon in the various war-areas, especially by the larvæ of blue-bottle and green-bottle flies ; whilst in East Africa, the troops, especially Indian, frequently suffered from African dermal myiasis due to invasion of the skin and subcutaneous tissues by the larvæ of *Cordylobia anthropophaga* or an allied species, a yellowish-grey fly about the size of a small blue-bottle, with blackish markings on the thorax and abdomen. **The Congo floor-maggot,** or larva of the fly, *Auchmeromyia luteola,* is the only dipterous larva known to suck blood. It is widely distributed in tropical and subtropical Africa, burrows in earth or dust, especially in the floors of native huts, and attacks those sleeping on the ground, sucking blood, but not, so far as is known, conveying any disease.

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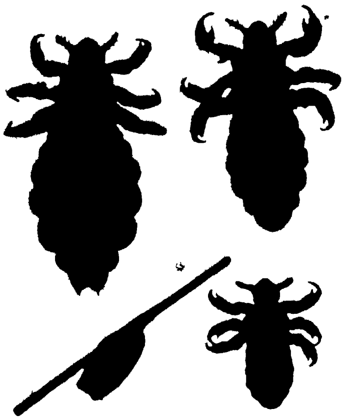
[1] It was noted that some severe infected wounds, when the site of such infestation, were " cleaned up " by the maggots, which attacked only the necrotic, and not the still living, tissues—the result being often more satisfactory than in similar cases in which the maggot-infestation had not occurred. Some use of this method of treating septic and necrotic wounds has been made by surgeons, more especially in America, but " treatment by myiasis " has not become popular in this country.

Some of the parasitic insects, *e.g.*, the pediculi or lice, and certain of the bugs, have become much degraded in structure in consequence of their parasitic habits, the wings, characteristic of non-parasitic hemipterous insects, having disappeared.

FAMILY : PEDICULIDÆ OR LICE

Infestation with Lice is known as **Pediculosis** or **Phthiriasis.**

PEDICULUS CAPITIS or Head-louse. The male measures from 1 to 1·5 mm and the female from 1·8 to 2 mm. in length, the colour varying from light grey to dark brownish-black. The operculated ova or " nits " are minute, white, ovoid, or pear-shaped bodies, visible to the naked eye. They are attached to the hairs and hatch in about a week, and the young insects mature in from three weeks to a month, the adult being somewhat oblong in shape. Severe irritation of the scalp may be set up, with the formation of pustules, impetigo-like crusts, etc., due largely to scratching and the resulting secondary bacterial infection, which may also involve the cervical lymph-nodes. Children especially are liable to attack.



Female. Male.

Ovum or " Nit." Larva.

FIG. 245 *Pediculus capitis* or head-louse. × 10.

PEDICULUS CORPORIS (Syn. *P. vestimenti*). The **Clothes-louse** or **Body-louse** lives upon the surface of the body and breeds in the clothing next the skin as well as on the skin itself. It lives by sucking blood and causes wheals with a central point of hæmorrhage at the site of the bite—often leading to the production of severe eczema due to the irritation of some toxic substance which it injects when it bites, to the scratching induced by the itching, and to secondary bacterial infection. It attacks all ages, but especially adults, more particularly aged and debilitated persons. It may produce serious anæmia in weakly children.

PHTHIRIUS INGUINALIS (Syn. *Pediculus pubis*). This variety, known as the **Crab-louse,** lives on the hairy parts of the body (with the exception of the scalp) and is found especially in the pubic region. It occasionally attacks the eyelids, producing a marginal blepharitis. The male measures 0·8 to 1 mm. and the female about 1·1 to 1·2 mm. in length. The severity of the lesions

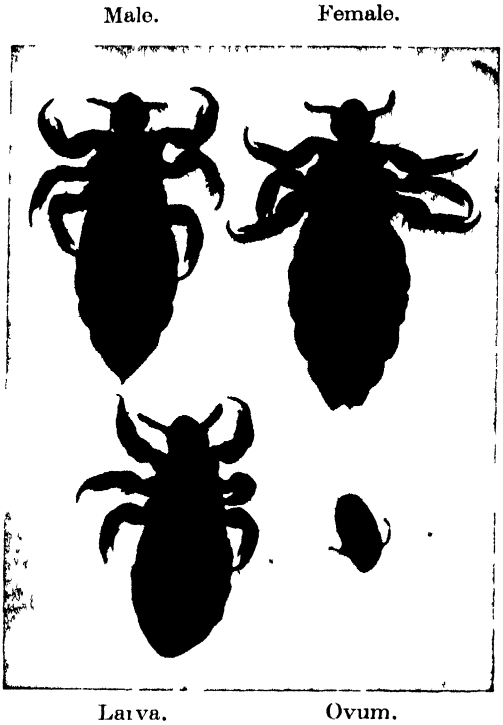


Fig. 246 *Pediculus corporis* (*P. vestimenti*), clothes-louse or body-louse. × 10.

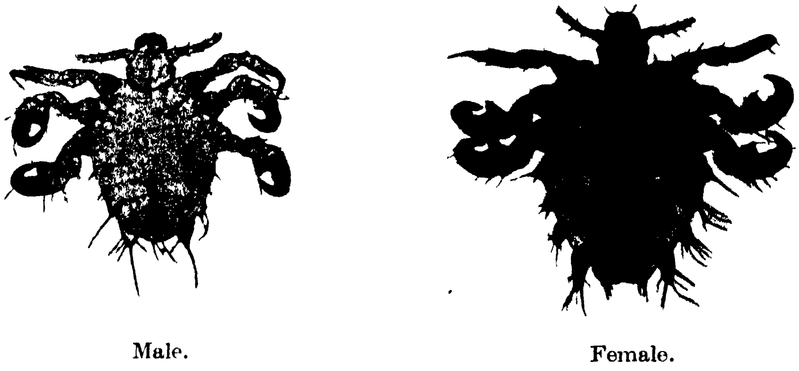


Fig. 247. *Phthirius inguinalis* (*Pediculus pubis*), or crab-louse. × 17.

varies in different cases. In some, the irritation may be severe and lead to the production of eczema.

Lice act as carriers of typhus, relapsing fever (p. 373) and trench-fever. **Trench-fever** has long been endemic in Poland, where it has been known as "febris quintana" or "five-day fever," or, from its prevalence in the Province of Volhynia, as "febris volhynica." During the War of 1914–18, trench-fever was spread throughout Europe by lice-infested German soldiers. The specific infective agent is *Rickettsia quintana.* In Sir David Bruce's Committee Report on the Louse and Trench-Fever,[1] it is stated amongst other important conclusions that the bite alone of the infested louse does not produce the disease, but that the experimental results were positive if the excreta taken from such lice are scratched into the skin, the incubation-period averaging eight days. The infection is therefore from the contents of the alimentary canal, which may either be deposited by the insect, or squeezed out by the patient in the process of scratching, and so inoculated into the bites and scratches in the skin. It is also noted that lice will leave a febrile patient and migrate to one with a normal temperature. It is probable that the method by which the *Spirochæta recurrentis* (p. 373) is inoculated is similar to that just described for trench-fever.

CIMICIDÆ OR BUGS

CIMEX LECTULARIUS—(Syn. *Acanthia lectularia*)—the **Common Bed-bug** or **House-bug,** is mahogany-brown in colour, measures 4 to 5 mm. in length and about 3 mm. in breadth, and is flattened as seen from above, hence the term "mahogany-flat" aptly describes it. It lives in bedding, furniture, etc., in crevices of which it lays its eggs. These hatch out in a week or ten days, the

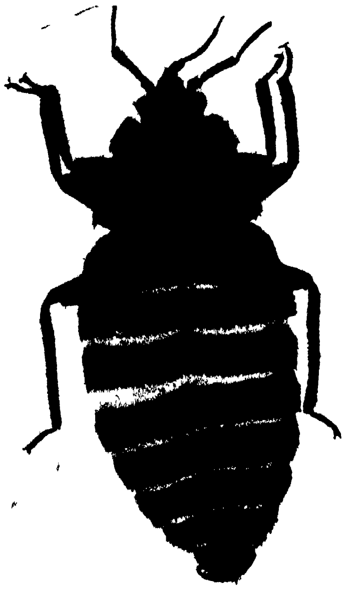


FIG. 248. *Cimex lectularius, Acanthia lectularia,* or common bed-bug (male). × 10.

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[1] *British Medical Journal* (1918), i, 353–4.

larva moulting its skin five times as it grows into the adult in about eleven weeks or less. One feed of blood occurs before each moult and before the laying of the eggs. These parasites attack man usually during the night.

Bugs are credited with transmitting various diseases, and experimentally they can be made to harbour various parasites, *e.g.*, *Leishmania*, *Trypansoma lewisi* and *T. cruzi*. Under natural conditions they can transmit relapsing fever (*Sp. recurrentis*) and typhus fever. They are *not* carriers of kala-azar as had been surmised.

Triatoma megista (Syn. *Conorhinus megistus*), a bug of a different Genus from *Cimex*, is the vector for *Trypanosoma cruzi* in South America (p. 370).

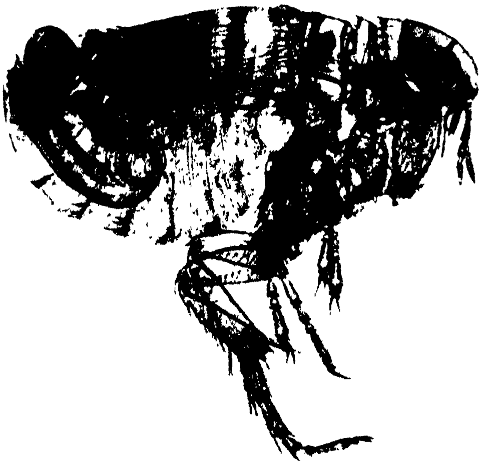

FIG. 249. *Pulex irritans* or common flea (male). × 22.

APHANIPTERA OR FLEAS

These are wingless members of this group of Insects, and are divided into two chief Families, the **Pulicidæ** or **True Fleas,** and **Sarcopsyllidæ** or **Jiggers.** The females of the latter Family, when fertilised, burrow under the skin of their hosts.

The eggs of fleas are ovoid, smooth and white, about 0·5 mm. in length, and are laid on or under the ground, on floors, carpets, rugs, etc., or in the nests of the animals they infest. In warm weather they hatch out in less than a week, but in cold countries incubation may occupy two or three weeks. The larvæ are pearly white in colour and are composed of fourteen segments without legs, but can move about actively. They mature, with usually three moults, in about a fortnight, and then undergo pupation of one to three weeks in a cocoon.

In addition to sucking blood and causing considerable irritation, fleas, especially those of the rat and other rodents, are of importance as carriers of plague.[1] The rat-trypanosome and certain tapeworms in their cystic stage, and possibly the infective agents of other diseases, are also carried and transmitted by fleas. It is important to note that fleas cannot jump more than 4 or 5 in., a fact that can be utilised for protecting experimental laboratory animals against infection by them. Most fleas infest more or less specific hosts. When these become diseased or die, the parasite may, however, attack other varieties of host if no specific hosts are available. Thus, when rats or other animals die of plague, the infected fleas may transfer themselves to man, whom they may thus inoculate with the bacillus of bubonic plague.

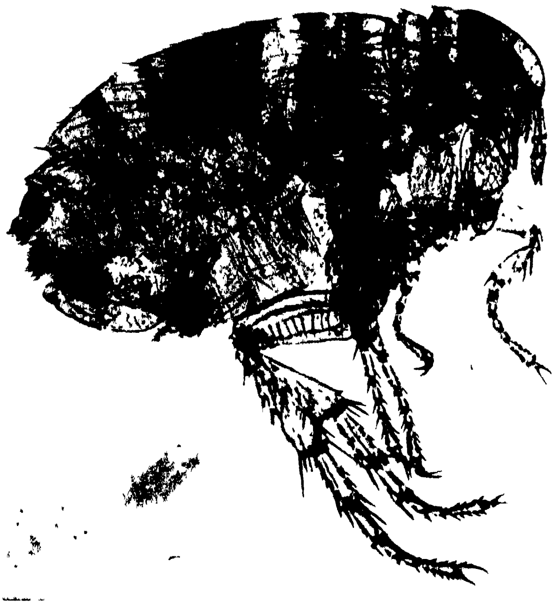

FIG. 250. *Pulex irritans* or common flea (female). × 22.

PULEX IRRITANS or Common Flea. The male is from 2 to 2·5 mm. and the female about 4 mm. in length. They are reddish-brown in colour, and the flattened body and legs are covered with fine hair-like bristles. The ova are barrel-shaped. The larva is an elongated, segmented body without legs. *P. irritans* is also found on the dog, cat, rat, badger and other animals, as well as on man.

XENOPSYLLA CHEOPIS—(Syn. *Lœmopsylla* or *Pulex cheopis*)—the **Common Rat-flea** of tropical countries has been transported to every country where the rat is found. This insect-parasite is of vast importance in connection with the spread of bubonic plague, of which it is the principal vector. It can convey the plague bacilli, not only from animal to animal, but from infected rats to man, as this species of flea will also attack the human subject. The flea itself does not appear to suffer in health from the bacilli which it harbours in its alimentary canal.[1] It is apparently its excrement which carries the infection, and this becomes inoculated into the bites or scratches on the human skin. This flea can act also as a transmitter of a form of typhus fever.

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[1] *B. pestis* (*Pasteurella pestis*) can be carried by the rat-fleas *Xenopsylla cheopis* and *Ceratophyllus fasciatus*, and *Hoplopsyllus anomalus*, a parasite of squirrels and rats, as well as by *Pulex irritans*.

Flea-bites usually show as small bleeding points surrounded by an area of erythema, and, in delicate skins, a wheal may also develop, produced by an irritating substance introduced by the flea. A more generalised urticaria sometimes develops after the introduction of this poison.

SARCOPSYLLA PENETRANS or Sand-Flea—(Syn. *Dermatophilus* or *Pulex penetrans*, or "**Jigger**," "**Chigger**," or "**Chigoe**")—is an important parasite in some parts of Central and South America, especially Brazil, the West Indies, Africa, India and elsewhere. The males and unimpregnated females are minute reddish-brown insects about 1 mm. in length. The male rarely attacks man. Only the female when impregnated becomes endoparasitic, swelling in her burrow to about the size of a small pea. Her abdomen becomes enormously distended with ova. After impregnation, she burrows beneath the skin, especially on the soles of the feet and between the toes, laying her eggs and causing inflammation and ulceration. Abscesses form, and serious secondary infections such as tetanus may supervene. The female lives head downwards in her burrow, the posterior segments of her body blocking the opening, through which the ova are expelled. After this process is complete, the female is herself expelled by the ulceration which ensues. Sometimes several hundred such parasites may be found on a single host. Pigs and other animals are attacked as well as man.

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[1] The following description of the method of inoculation is given in the official "Memoranda on Medical Diseases in the Tropical and Sub-Tropical War Areas" (1919), p. 203 : "It might be supposed that the flea inoculates the bacillus when it bites. This is not the case. What really happens is very interesting. The flea sucks up blood containing plague bacilli. These multiply at its proventriculus, and the bacillary mass eventually extends into the œsophagus, thus blocking the entrance of the stomach. The starved flea makes violent efforts to get more blood, and the œsophageal contents regurgitate, thereby infecting through the skin lesion the healthy person on whom the flea is trying to feed. The flea itself does not necessarily die from the obstruction, but it is apt to do so if the weather is dry, presumably from lack of fluid. . . . Infection may also occur from the bacillus-containing fæces of the flea voided on the skin and rubbed into the wound. The rat-flea may remain infective for 43 days."

CHAPTER XV

DISEASES DUE TO VITAMIN-DEFICIENCY

DEFICIENCY-DISEASES

In the case of the endocrine glands it has been shown that disease may result either from overaction of a particular gland, *e.g.*, thyroid : or from its underaction. This conception of disease arising from deficiency of an essential factor is well exemplified in the case of the vitamins, indeed, the diseases related to vitamins are usually grouped under the heading of " Deficiency-Diseases." This is an appropriate term for the great majority of vitamin-defects, for, as yet, only one example of overactivity, that of vitamin D, has been recognised, and then only where great excess of this substance has been administered.

Vitamins have been extracted from many foodstuffs and purified, and some are now prepared synthetically.

Whilst the several vitamins have special functions in the nutrition of particular tissues, some of them possess the common function of favouring growth of the body as a whole, and their withdrawal leads to an arrest of growth and a failure to maintain the normal body-weight. E. and M. Mellanby have shown that deficiency of certain of the vitamins allows of a damaging action by a normal foodstuff (p. 440), or conversely that the presence of the vitamin promotes normal growth and utilisation of the foodstuff in question.

Knowledge about vitamins is constantly increasing, and research is continually adding new facts and amending the interpretation of former findings. At present this is particularly true in regard to vitamin B, or, as it is now called, the vitamin-B complex. The various vitamins will be discussed in a more or less arbitrary order, taking first the fat-soluble group, A, D, E and K.

VITAMIN A. This vitamin, a hydrocarbon, is present in many animal-fats, *e.g.*, cod-liver oil, and can be elaborated by the liver from the yellow lipochrome, **carotene** (carotin) formed in many plants. It is stored in the liver, and as long as there is a store of it an animal can survive and grow without further external supply.

Vitamin-A Deficiency. Deprivation of this vitamin does not produce disease till the natural store in the body is exhausted. Growth is then arrested and degenerative and inflammatory changes occur in various epithelial-lined areas (" xeroses "). This is most obvious in the conjunctiva as " xerophthalmia," a condition of conjunctivitis with swelling and redness of the lids and opacity of the cornea—" keratomalacia " : ultimately the eye may be destroyed by panophthalmitis. The primary change is one of atrophy of the epithelium followed by surface keratinisation. It occurs, not only in the conjunctiva and cornea, but also in the lacrimal ducts, in the nasal passages, the tracheal and bronchial epithelium (in which a metaplasia to a squamous type may be seen), in the epithelium of the renal pelvis and urinary bladder, the genital tract, and on other epithelial surfaces. Enamel-formation is arrested and irregularity of the dentine occurs in teeth. These changes have been studied in experimental animals, but similar phenomena have also been observed in children.

As a sequel to these pathological alterations in epithelial surfaces due to vitamin-A deficiency, there is an increased liability to infection. In xerophthalmia there are the initial changes in the conjunctival and corneal epithelium and blocking of the ducts of the lacrimal glands owing to the keratinisation of their epithelium. The eye is thus deprived of the normal secretions of these glands and, owing to the alteration in its epithelium, it becomes vulnerable to infection. The epithelial changes in the respiratory and genito-urinary tracts also allow of the entrance and proliferation of bacteria, so that infections—bronchitis, bronchopneumonia, and pyelocystitis—are common. From the fact that vitamin A prevents such infections it has been regarded as " the anti-infective " vitamin ; this is not due to any specific action upon the micro-organisms themselves, but to its presence promoting such a healthy condition of the epithelial covering that access of micro-organisms is prevented. Vitamin A is an important constituent in the retinal pigment, in which it is essential for the regeneration of the visual purple. Deficiency of vitamin A leads to the occurrence of "night-blindness" (hemeralopia), which can be cured by suitable administration of the vitamin.

VITAMIN D (the " anti-rachitic vitamin ") is present in some animal-fats, fish-liver oils especially being rich in it. It can be prepared (as " calciferol ") from various " sterols," and it is formed by the action of ultra-violet rays on a number of these substances. Like vitamin A, it is to some extent stored in the body, so that the effect of deprivation of it in the diet is not immediate. Its presence is necessary for the efficient absorption and assimilation of calcium and phosphorus from the bowel.

Deficiency of Vitamin D is manifested by conditions such as **Rickets** (pp. 240 and 1214–18), in which absorption and utilisation of calcium is seriously interfered with, or is at a low level. **Tetany** may develop owing to increased irritability at the neuro-muscular junctions. In the teeth, defective formation of enamel and dentine is seen, and is usually complicated by superadded bacterial infection which obtains entrance through the defective surface-layers of the teeth, the protective powers of which are lost—with the production of dental caries.

The defective development of the bones and teeth may be modified by the character of the cereals of the diet. Mellanby states that refined wheat-flour is less harmful than whole-meal; and that, in the absence of a sufficiency of vitamin D, oatmeal can be responsible for serious bony and dental changes. When the vitamin is present in adequate amount, calcification of bones or teeth proceeds normally on a diet containing any cereals. It would thus appear that there is a positive element in the cereal, as well as the negative factor of the vitamin-deficiency concerned in the production of the lesions. Various other ill-effects may ensue from deficiency of vitamin D, such as delayed as well as defective dentition, delayed union of fractures and certain circulatory disorders such as chilblains (p. 186).

Osteomalacia (pp. 240 and 1211). This is a deficiency-disease in the adult resembling in its causation rickets in the child. It is due to deficient intake of vitamin D, usually combined with a diet also inadequate in calcium and phosphorus. It is encountered in areas, such as parts of China, where the inhabitants are on the verge of famine, their diet being insufficient in both amount and quality. The pregnant female especially suffers, as a diet that barely suffices for the mother is still more inadequate for mother and fœtus combined. The usual features of osteomalacia—softening and rarefaction of the bones—occur in the mother, whilst the child may show changes closely resembling rickets (" fœtal rickets," p. 1214 *et seq.*).

Hypervitaminosis. So far as at present known, this condition is possible only with great excess of vitamin D. When very large doses are administered to animals, they become ill, with loss of weight and diarrhœa, and may die within from fourteen to forty days. There is considerable deposition of calcium ("metastatic calcification"—*cf.* p. 484) in the arterial coats, the larger vessels being involved first, and, later, the smaller arteries: and also in the heart-muscle, stomach-wall and renal tubules. Renal calculi may be formed owing to the increased excretion of calcium and phosphorus in the urine. During life, the blood-calcium- and phosphorus-contents are raised. The picture present in hypervitaminosis resembles that seen in hyperparathyroidism (p. 838). The amounts and relative proportions of calcium and phosphorus in the diet modify the changes produced: a high calcium-content leading to excessive deposition of calcium in the tissues, a low calcium favouring less deposit, but tending to lead to a withdrawal of calcium from the bones (*cf.* p. 838). Vitamin D and the parathyroid hormone may thus produce similar results though their line of action is slightly different, vitamin D being concerned primarily with assimilation, and parathyroid with utilisation, of calcium and phosphorus.

A fatal result in a few cases in children has been recorded where large doses of vitamin-D preparations have been given over a considerable period. In such cases, additional factors which may have aggravated the effects have been present, such as prolonged exposure to sunlight or the presence of tuberculous disease. The patients exhibited febrile symptoms, loss of weight, albuminuria and pyuria; at post-mortem, calcification was found in the renal tubules, similar to that seen in the experimental animal, but not a general calcification. During life, hypercalcæmia and hyperphosphatæmia have been noted.

VITAMIN E ("α-tocopherol,"[1] the "anti-sterility vitamin"). This fat-soluble vitamin is found in plant-tissues, particularly in green leaves and the seed-embryo, wheat-germ being a common source. It can be stored in animal tissues and has been found in normal muscle—its absence being suspected to contribute to certain disorders of both nerve and muscle (pp. 1011, 1016 and 1244). The presence of this vitamin is necessary for fertility, deprivation of it leading to sterility. The effects differ in the two sexes. Experimentally, in the **male** rat, absence of vitamin E from the diet for a period varying from seven to fourteen weeks or longer, renders the spermatozoa, though still present, incapable of fertilising the ova. Later, they disappear altogether. The testis shows a gradual degeneration of the germinal cells, which finally disappear; and there may be a concomitant increase of the interstitial connective-tissue. Once this change has taken place it is irreversible, *i.e.*, there is no recovery even if vitamin E is subsequently administered. In the **female** rat the effects are of a different order. Ovulation, fertilisation and implantation can occur normally, but, instead of the fœtus continuing to grow and develop, it dies after a few days and is reabsorbed, the placenta being absorbed later. This state persists as long as the vitamin is absent, but fertility can be restored by its administration. The condition in the female is thus reversible. Deficiency of this vitamin does not appear to affect the general health of the animals, apart from the effects on reproduction, and, except for its possible effects on neuro-muscular nutrition (*see* p. 1244), no morphological changes have been yet detected elsewhere in the body.

The application of our knowledge of these experimental results to man is still largely in the theoretical stage, especially as regards the male. In the case of the female there have been recorded cases of sterility, which, though not due to any of the usual recognised causes, have apparently been cured by the administration of vitamin E.

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[1] "Synthetic racemic α-tocopheryl acetate," ($C_{31}H_{52}O_3$), has been adopted as the international standard for vitamin E.

VITAMIN K.—the "Koagulations-Vitamin" of Henrik Dam and Schönheyder, of Copenhagen (1936)—so named because it is concerned with coagulation of the blood (pp. 161 and 587). It is one of the fat-soluble vitamins and is widely distributed in nature, being found in the livers of various mammals and fish, in vegetables such as alfalfa, spinach, tomatoes and carrot-tops, in human fæces (in the new-born infant it is lacking until the gut acquires an intestinal flora), as well as in putrid-fish meal, the action of certain bacteria of putrefaction being necessary to its formation. It is absorbed from food in the alimentary canal—where possibly it may, in the case of mammals, also be synthesised—and the presence of bile favours its absorption. In patients suffering from obstructive jaundice, hæmorrhages into the skin and mucous membranes are frequent, clotting-time is delayed and the prothrombin-content of the blood is low. The blood of new-born infants is also often lacking in prothrombin, this deficiency being an important predisposing cause of neo-natal, and especially of intracranial, hæmorrhage.[1] Administration of vitamin K, together with bile-salts to facilitate its absorption, leads to a prompt rise in the prothrombin-content and arrest of the hæmorrhagic condition (p. 588).

The **water-soluble vitamins** comprise the B-complex and C. Of these, C has been identified as ascorbic acid and is now available ; whilst the B-complex is gradually being disentangled, several of its constituents having been identified and isolated in pure form.

VITAMIN C. This has been called the "antiscorbutic vitamin" because of its important *rôle* in the prevention of scurvy or scorbutus. It has long been known that fresh vegetables or fresh fruit in the diet will prevent scurvy, the scourge of the early navigators, and Lind in 1747 described the rapid curative effects of fresh oranges and lemons. The experimental study of the disease in animals is much more recent, dating from 1907, when A. Holst and his co-workers produced the disease in the guineapig. It was shown by Szent-Györgyi in 1928 that vitamin C is identical with **ascorbic acid** (at first named "hexuronic acid" and now also known as "cevitamic acid") and is present in the adrenal cortex. Since then (1933 and 1934), it has been synthesised.

Animals such as cows, rats and mice, seem capable of forming this substance in their tissues and so can live and thrive without any supply in the food, but man, monkeys and guineapigs require to ingest it preformed in their diet and can then store it in their tissues, especially in the suprarenal cortex, which may contain three times as much vitamin C as does orange-juice. Because of this, deprivation-effects do not show until about three weeks in the case of the guineapig and four to six or eight months in man.

Vitamin C is essential for the development and maintenance of the intercellular substances formed by mesenchymatous cells ; it is also essential for the processes of normal repair. In its absence, fibroblasts may grow, but cannot produce their collagen-fibrils; and the matrix of connective tissues and the supporting reticulum of vascular endothelium become absorbed. **In scurvy,** the blood-vessels become more permeable, and hæmorrhages are common. This has hitherto been attributed to deficiency or absence of **vitamin C** in whole or in part ; but it is now believed that more than this deficiency of ascorbic acid is involved, and, from the investigations of Rusznyák and Szent-Györgyi [1] and their collaborators, the deficiency of certain **flavones** (" citrine ") in scorbutogenic diets also plays an important part. These flavones, present in lemon-juice and similar substances, act in a capacity similar to that of a vitamin, and they have therefore been named **vitamin P,** because of their influence upon the **P**ermeability of the walls of capillaries (p. 137).

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[1] The full-term infant has usually only about one-sixth to one-third of the proportion of prothrombin of the adult, and premature infants much less. A simpler member of this class of compounds, 2-methyl-1 : 4-naphthaquinone, has now been artificially synthesised, and can be administered to the mother before delivery or to the infant immediately after birth.

In young growing bone, when the vitamin-C complex is deficient, the cartilaginous and osseous matrix fails to develop, and that already present becomes atrophic and eventually reabsorbed, and separation of the epiphysis or fracture of the bone may easily result. The bone-marrow undergoes atrophy and becomes replaced by a hyaline or mucinoid type of connective tissue (p. 608) often mixed with hæmorrhage.

The teeth suffer in an analogous fashion. This has been studied in some detail in the guineapig, in which animal the central incisors normally show a steady and continuous growth. In vitamin-C deficiency this growth is arrested, and, in addition, there is degeneration and disintegration of the enamel and dentine, together with hæmorrhage into the pulp and formation of osteoid tissue in the latter extending outwards towards the degenerating dentine.

Scurvy in the human adult may be acute or chronic, depending on the degree of deficiency. Usually, the disorder is of slow development, with increasing weakness and scattered hæmorrhages in the subcutaneous and submucous tissues and muscles. The gums become spongy and the teeth loosened and may fall out, mixed bacterial infection supervenes and a foul condition of the mouth results (p. 705). The patient becomes progressively weaker and—if untreated—will die of exhaustion or, more commonly, of some intercurrent infection.

Anæmia is present and is usually of the orthochromic normocytic type (secondary anæmia) with slight leucopenia ; cases of megalocytic hyperchromic type have been recorded, resembling Addisonian anæmia, except for a moderate reticulocytosis ; and, in the treatment of Addisonian anæmia itself (p. 653), a sufficiency of vitamin C should always be assured. Vitamin C will excite a reticulocytosis and help in restoring the blood-picture to normal, whilst the undue capillary permeability can be lessened by the administration of vitamin P in the form of " citrine."

In scurvy, the vitamin C (ascorbic acid) stored in the tissues has become exhausted. This may be detected by examination of the urine. Normally there is excretion of ascorbic acid, varying with the intake ; but in scurvy none is excreted and the administration of ascorbic acid is followed by its retention in the tissues until the normal store has been replenished. Examination of the urine before and after administration of a fixed amount of ascorbic acid, in order to estimate its excretion and utilisation, is, therefore, used as a test, not merely for frank clinical scurvy, but also for minor degrees of vitamin-C deficiency. The tendency to hæmorrhage has also been utilised for test-purposes, the general principle being to congest the arm by a tourniquet, when there results a crop of petechial hæmorrhages from the congested capillaries if there is deficiency of vitamin C or, more probably, of vitamin P ; but similar hæmorrhages may occur in esssential thrombocytopenia (p. 669) where there is no evidence of vitamin-C deficiency.

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[1] *Nature,* 1936, **138,** 27 and 796 ; 1937, **139,** 326.

Scurvy is apt to occur if artificially-fed infants are not given fresh fruit-juice. The child ceases to thrive, and suffers from hæmorrhages (most frequently under the periosteum of the long bones) together with the other abnormalities of defective ossification, etc., to which reference is made on pp. 440–41. The condition is known as "scurvy-rickets" (p. 1218).

In many pathological conditions, *e.g.*, tuberculosis, rheumatic fever, hæmolytic streptococcal infections and peptic ulcer, low values have been noted for the ascorbic-acid concentration in the blood ; and the administration of a larger amount than normal is required in order to raise the value to the normal level, which is usually regarded as being from 1·2 to 1·5 mgr. per cent. in normal healthy individuals.

VITAMIN-B COMPLEX.[1] Under this term are included a number of water-soluble substances obtained from such sources as yeast, plant-embryos and eggs. All the constituent elements of the complex are essential for growth, but several have been separated and shown to be concerned more particularly with functions such as the maintenance of integrity of nervous tissue, of the alimentary tract, and of skin. In the earlier stages of investigation of the B-complex, two elements were identified—B_1 (or F), the **anti-neuritic**-factor : and B_2 (or G), the **anti-pellagra**-factor (also known as **pellagra-preventing,** or **P.P.,** and **anti-dermatitis**-factor). Of these, B_1 has been isolated in crystalline form from yeast and has now been synthesised.

B_2 is itself a complex, and includes (i) riboflavin, (ii) nicotinic acid, (iii) vitamin B_6 and (iv) the substances grouped under the name "filtrate-factor," connected with the prevention of certain forms of anæmia. Of these B_6 or "adermin," seems to be the anti-dermatitis-factor for the rat, and nicotinic acid the anti-pellagra-factor for man and dog. Of the others all that can at present be said is that they are not yet identified chemically, but seem to be necessary for growth of various animals and birds.

Vitamin-B_1 Deficiency. This has been studied experimentally, especially in the pigeon, by feeding on a diet of highly-milled or polished rice, *i.e.*, rice from which the husk and seed-embryo have been removed. The bird may exhibit an acute condition of opisthotonos and blindness—which is rapidly cured by adding the "millings" to the diet—or a more chronic condition of neuritis. Biochemical investigation has shown that this vitamin acts like a catalyst in the pigeon's brain whereby the utilisation of oxygen is made possible for the complete combustion of carbohydrate needed for the energy of nerve-tissue. In the absence of the vitamin, pyruvic acid and lactic acid result from incomplete oxidation of the carbohydrate. Pyruvate has been detected in the blood and cerebrospinal fluid of beri-beri patients.

In man, vitamin-B deficiency is the basis of the disease **beri-beri** (pp. 1180 and 1184). As long ago as 1897, a Dutch physician, Eijkman, working in Java, observed the relation between beri-beri and polished rice and Grijns suggested that a "deficiency" in the rice was the cause of the disease. The main features of the disease are polyneuritis, a dilatation of the heart, and œdema, all of which may be removed by the administration of vitamin B_1, either in the crude form of yeast, or as the purified crystalline substance, natural or synthetic.

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[1] "The Clinical Significance and Estimation of Blood Vitamin B_1," by E. N. Rowlands and J. F. Wilkinson, Manchester, *Brit. Med. Jour.*, 1938, ii, 878. See also Discussion on "Clinical Aspects of Vitamin-B Complex," Royal Society of Medicine, January 10th, 1939 (*Brit. Med. Jour.*, 1939, i, 129), and "Nutritive Value of White Flour with Vitamin B_1 added and of Wholemeal Flour," by Harriette Chick, Lister Institute, *Lancet*, 1940, ii, 511.

Other forms of polyneuritis (p. 1180 *et seq.*) may in reality be manifestations of a B_1 deficiency. Thus alcoholic neuritis occurs in the chronic alcoholic subject whose food is often rejected or poorly absorbed as the result of his habits. Examination reveals a reduction in the amount of B_1 present in the blood ; and treatment with this vitamin leads to amelioration. Various nutritional anæmias of the microcytic type may also be due to B_1 deficiency.

Vitamin-B_2(Complex)-Deficiency. Absence of the B_2 group leads to a series of changes such as dermatitis, anæmia, achlorhydria and even degeneration of the myelin of nerve-sheaths in the spinal cord. In dogs, a condition of glossitis (" black tongue ") is found. Of the group, lactoflavin has not been definitely incriminated as yet, but the absence of B_6 in rats and of nicotinic acid in man and the dog causes a condition of dermatitis.

Pellagra (p. 1076).[1] This is the disease in man which results from deficiency of the B_2 complex. It is a disease especially of the poor, in whom it develops gradually and appears as a dermatitis affecting the exposed parts—face, neck, hands and arms—which also become pigmented. Its distribution, on the exposed surfaces, is due to a sensitisation of the skin to sunlight. The cause of this is apparently an increased formation of porphyrin in the body. Rats deprived of vitamin-B_2 complex excrete a porphyrin-compound in their urine, and investigation of human cases of pellagra has shown a porphyrinuria which disappears after treatment with vitamin-B_2 complex. There may be intestinal symptoms such as diarrhœa, and nervous symptoms due to demyelinisation in the spinal cord (pp. 444, 1076–7 and 1157). The dermatitis results from atrophic changes in the skin, with resulting superficial keratinisation and areas of ulceration. The administration of yeast or of nicotinic acid can cure the condition or prevent its recurrence, though relapses may occur, and these are reported to have been cured by giving riboflavin (see above). Stannus believes that there is a synthesis of a "pellagra-preventing factor" in the stomach analogous to the production of Castle's factor in Addisonian anæmia (pp. 647 and 1076 *et seq.*).[1]

References. Various reports in the Medical Research Council Special Report Series, including No. 167. *Vitamins. A Survey of Present Knowledge*, 1932. In this is given the history of vitamins and numerous references to date of publication.

Annual Review of Biochemistry (1936), **5**, *The Water-soluble Vitamins*, p. 355, by H. von Euler, and *The Fat-Soluble Vitamins*, p. 379, by E. V. McCollum. *Ibid.* (1937), **6**, 335, *The Vitamins*, by C. C. and H. C. Sherman, and (1938), **7**, 305, *The Vitamin B Group*, by R. A. Peters and J. R. O'Brien ; 325, *Vitamin C* (*Ascorbic Acid, Cevitamic Acid*), by R. A. Peters and H. W. Davenport ; 335, *The Fat-Soluble Vitamins*, by J. C. Drummond.

American Medical Association : *The Vitamins : A Symposium*, 1939. E. V. McCollum, E. Orent-Keiles and H. G. Day: *The Newer Knowledge of Nutrition*, 5th ed., 1939. Society of Chemical Industry : *Vitamin E : A Symposium*, 1939 : H. R. Butt and A. M. Snell: *Vitamin K*, 1941. W. H. Eddy and G. Dalldorf : *The Avitaminoses*, 2nd ed., 1941.

In these annual reviews, the details of the biochemistry of the vitamins are given to date, with full references to the current literature. The whole subject of vitamins is being investigated so actively that many papers on all aspects are constantly appearing. The above references give a wide basis on which to build subsequent knowledge. The present trend is to emphasise the importance of deficiency in vitamins in a variety of diseases other than those primarily considered as avitaminoses. Individual dietary peculiarities and fads may produce clinical and subclinical forms of deficiency-disease as certainly as economic limitations or even famine.

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[1] See papers by Hugh S. Stannus, on " Pellagra," *Lancet*, 1940, i, 352 : and " Skin Manifestations in Diseases of Malnutrition (Deficiency Diseases)," *Practitioner*, 1941, **146**, 303.

CHAPTER XVI

DISEASES OF THE CIRCULATORY SYSTEM

Note. As cardiologists and clinicians in general have not yet agreed to adopt the new anatomical nomenclature which is being used in the teaching of students in many anatomical schools, we propose using the old terms, giving in the earlier pages their new equivalents in brackets, thus : **auricle (atrium), auricular appendage (auricle).**

SECTION I

DEVELOPMENTAL ABNORMALITIES OF THE PERICARDIUM, HEART, AND GREAT VESSELS

The main developmental abnormalities that are likely to give rise to clinical manifestations or to be discovered on post-mortem examination are the following :

1. Complete Absence of the Pericardium is rare, but imperfect development is occasionally found. **Pouches** in and from it are described, but these are merely protrusions of the serous coat, either into the cavity of the pericardium, or outwards through a thin or imperfectly developed fibrous coat.

2. The Ventricular Septum may be absent or it may be incompletely developed, leaving a single, undivided cavity or two cavities which intercommunicate either at the upper (or membranous) part of the septum or more rarely at the posterior part.

3. The Auricular (Atrial) Septum may be absent, or deficient only at its lower part. The most frequent abnormality is non-closure of the foramen ovale. Usually the opening is small, very oblique, and so valvular in character that there is little or no communication between the blood in the two auricles (atria). More rarely, the opening is directly patent, *i.e.*, the portion of the septum is itself absent in whole or in part, and there is thus a persistent communication, through which a mixing of the arterial and the venous blood takes place a defect which is sometimes combined with congenital stenosis of the pulmonary orifice.

4. Subdivision of the Right Ventricle is comparatively rare, and in it the ventricle is separated from its infundibulum by a muscular partition, the centre of which is perforated by a foramen varying in size. The cusps of the pulmonary valve may be normal, or they may be united, producing stenosis of the orifice. There may be an interventricular foramen just below the opening from the ventricle proper into the infundibulum. The ductus arteriosus and the foramen ovale may be patent. In an examination of such cases, Keith,[1] to whose work we are greatly indebted for our information on these malformations in the heart, found that the fibrous margin of the "ostium infundibuli" was covered by vegetations.

5. Congenital Pulmonary Stenosis. Though some examples of this are attributed to fœtal endocarditis, most, if not all, are the result of an arrest of development of the infundibulum. The endocardium may be embryonic (fibro-cellular) in character or it may be thickened in considerable degree. In the majority of cases, the cusps are fused, and in some they are imperfect. The pulmonary orifice may be much narrowed. An interventricular foramen is generally present.

If the stenosis occurs during an *early* period of development, the increased pressure in the right ventricle forces the ventricular septum to the left side, the aorta comes to open partly from the right ventricle, and the upper portion of the septum thus remains incomplete. In the same way, the increased pressure in the right auricle (atrium) interferes with the closure of the foramen ovale. Thus, in cases of congenital narrowing of the pulmonary artery, there are frequently associated with it an incomplete ventricular septum and a patent foramen ovale. If the stenosis takes place *after* the ventricular septum is complete, increased work is thrown on the right ventricle, and it becomes hypertrophied, sometimes in considerable degree. The right auricle (atrium) becomes dilated, and the foramen ovale remains patent. If this patency is pronounced, there usually result enormous dilatation of both auricles (atria), especially of their auricular appendages (auricles) and hypertrophy of the left ventricle. The ductus arteriosus, in such cases, frequently persists as an open channel.

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[1] See footnote on p. 702.

6. **Stenosis of the Aorta** is rare, but may be found at a point between the left subclavian artery and the opening of the ductus arteriosus, at the origin of the aorta and at, or beyond, the junction of the ductus arteriosus. There may be complete stenosis (atresia) of the orifice or the aorta may be narrowed (**coarctation**) in the region between the ductus arteriosus and the subclavian artery or just distal to the obliterated ductus (see p. 448).

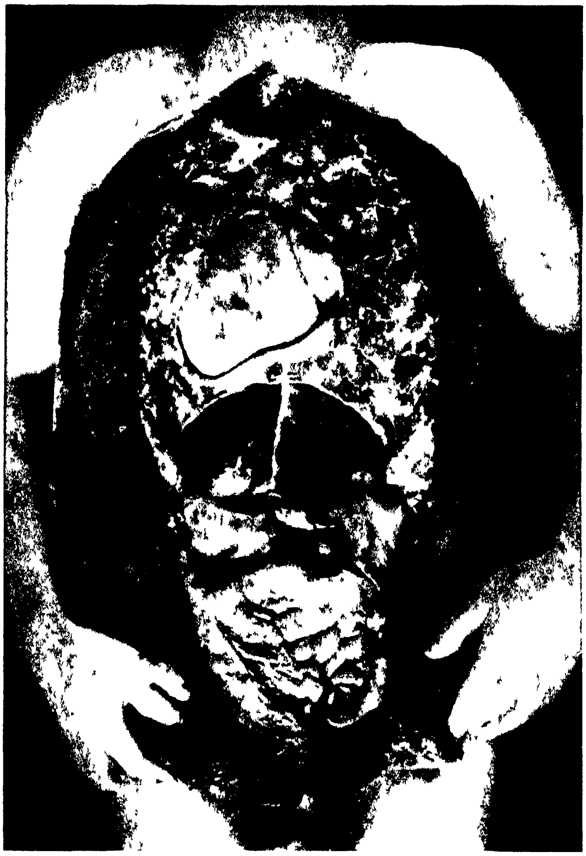

FIG. 251. *Transposition of Viscera.* Note apex of heart on the right side, stomach on the right side, the cæcum and appendix are transposed to the left side. Note also the double thumb on the right hand. (From a case of the late Sir Thomas R. Fraser.)

7. **Abnormalities in the Cusps of the Valves.** The cusps of the pulmonary and aortic orifices are sometimes abnormal in number or in size. There may be only two cusps —one generally being larger than the other, and sometimes showing evidence of partial division. Of the three cusps generally present, two may be large and the third rudimentary ; or there may be four, or even more.

Fenestration of the lunulæ is common, and adhesions between the cusps or between auriculo-ventricular (atrio-ventricular) curtains are generally due to endocarditis.

8. **Abnormalities in the Large Vessels.** Doubling of the aorta, due to a persistence of the two developmental arterial arches, is occasionally found ; or the right arch may remain and form the aorta instead of the left. This is generally the case in dexiocardia, but may occur independently of that condition. In exceptional cases, the left superior vena cava persists instead of the right and the pressure of the heart upon it may produce obstruction. The

aorta sometimes takes origin from the infundibulum of the right ventricle, and the pulmonary artery from the left ventricle.

9. **Malpositions of the Heart** are rare. There may be complete transposition—dexiocardia—but, in such cases, there is generally, in addition, transposition of the other viscera (Fig. 251, p. 447).

Some of the defects mentioned above are incompatible with continued extra-uterine life—for example **infantile coarctation,**[1] in which the constriction of the aorta is proximal to the ductus arteriosus, between it and the left subclavian artery. This form is, therefore, seen only in young infants and in still-births. In the type sometimes found in persons who live to become **adults,** the narrowing is at or just distal to the ductus, and the lower part of the body is nourished by a collateral circulation between the subscapular and internal mammary arteries and the intercostals and epigastrics respectively. These collaterals may be greatly dilated, may be visible along the borders of the scapula, and sometimes grooving of the ribs is present. High blood-pressure is associated with this defect. **Patent ductus arteriosus** is not rare as an isolated congenital lesion and may throw additional strain upon the heart, increasing the work of the left ventricle to such an extent as to produce cardiac failure. Other congenital abnormalities give rise to cyanosis from admixture of arterial and venous blood, and frequently death occurs in the early years of life from heart-failure.

SECTION II

DISEASES AND INJURIES OF THE PERICARDIUM AND HEART

In considering diseases of the heart, it is convenient to study separately and in order those of the **pericardium,** the **endocardium** and the **myocardium,** but it should be remembered that in the commonest infective process—rheumatic fever—there is a general infection of the fibrous tissue and endothelium of the heart. This general carditis (**pancarditis**) may attack, in the first instance, the myocardium, endocardium or pericardium, or there may be a reaction in each about the same time.

I. PERICARDIUM

Developmental abnormalities of this structure are referred to on p. 446.

Injuries. *See below, under* "Hæmopericardium."

Hydropericardium. On post-mortem examination, a small quantity of transuded fluid is normally present in the pericardial sac. This may be increased in slight degree (to a few ounces) before death, or there may be a great increase, producing a condition of hydropericardium. The nature of the fluid depends largely on the cause leading to its presence. The commonest examples of hydropericardium are seen in diseases of the kidneys, and in the "water-logging" of chronic heart-disease. In such conditions, the fluid is watery and of a light straw-colour, and usually contains little albumin. It may, however, be bile-stained, or it may contain blood derived from dilated vessels which have ruptured. More rarely, the fluid is milky in appearance and contains a large proportion of chyle (p. 425). This is seen in cases where there is some pathological condition of the thoracic duct or of its tributaries.

Hæmopericardium. Large quantities of blood may be found in the pericardial sac as the result of penetrating wounds of the heart: or from rupture of the organ, with or without obvious evidence of external injury, from severe blows upon, or from compression or crushing injuries of, the chest, or from the blast of explosives, which may produce varying degrees of contusion of the myocardium, rupture of the muscle or of valves, as well as lesser degrees of trauma.[1] With or without external injury, hæmopericardium may also result from the rupture of an aneurysm either of the intrapericardial portion of the aorta or of a coronary artery. " Spontaneous " rupture of the heart occurs occasionally as a sequel of degeneration and arteriosclerotic narrowing of the coronary arteries, with associated fatty degeneration and atrophy of the muscle-fibres, or from blocking of the coronary arteries, with resulting infarction of a portion of the heart-wall. Most commonly, the rupture is in the wall of the left ventricle, on its anterior aspect near the septum. It is ragged in appearance, and runs usually in the direction of the muscle-fibres. The amount of blood in the pericardial sac varies from a few ounces to a quart or more. Other causes giving rise to an accumulation of blood, or of blood-stained exudates, in the pericardium are mentioned under hæmorrhagic pericarditis on p. 450. Petechial, and sometimes larger, hæmorrhages are seen, especially in the subepicardial tissues in anæmic conditions and in toxic and bacterial diseases. In deaths from asphyxia (*e.g.*, drowning), small hæmorrhages may be present (" Tardieu's spots "). These subepicardial hæmorrhages occur mainly at the base of the ventricles and along the vessels.

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[1] **Latin,** *coar(c)tātio,* compression, from *coar(c)tāre,* to compress, and *artāre* or *arcēre,* to hold together.

" **Milk-spots** " are irregular, whitish, thickened patches of fibrous tissue, seen most commonly on the anterior surface of the right ventricle, or on the anterior surface of the left ventricle towards the apex. They are found less frequently on the posterior aspect of the left ventricle near the base of the heart. They may be merely opalescent thickenings of the epicardium, or may be distinctly fibrous and even almost " cartilaginous " in consistence. In many instances they are the remains of a localised pericarditis ; but their situation, and their greater frequency in hearts which are, or have been, hypertrophied or dilated, lend support to the view that they may be caused by a constant and increased degree of friction, giving rise to irritative overgrowth of the epicardium. In chronic renal disease, these milk-spots sometimes become œdematous. More generalised thickenings of the epicardium are common over dilated auricles (atria) and auricular appendages (auricles), or along the lines of dilated or atheromatous coronary arteries.

INFLAMMATION :—

Acute pericarditis (Figs. 7 and 9, pp. 22 and 24) has always, for its cause, some bacterial, viral or toxic irritant. It occurs most commonly during an attack of rheumatic fever, or allied conditions such as chorea, acute tonsillitis, etc., but it is also common in pneumonia, especially in children, and in certain acute infective fevers, and in septicæmia and pyæmia. It also supervenes, though more rarely, and generally as a terminal event, in many other diseases. Acute pericarditis arises also by local extension of inflammation from a neighbouring area. Thus, inflammation of the pleura, lungs, mediastinal cellular tissue or lymph-nodes may involve the pericardium secondarily. Inflammation of the myocardium more rarely spreads to the pericardium, but abscesses in the heart-wall in pyæmia, or abscesses in the mediastinum, or in the ribs, sternum, or elsewhere, may rupture into the pericardial sac and set up an acute suppurative pericarditis.

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[1] " Contusion of the Myocardium," by Hugh Barber, Derbyshire Royal Infirmary, *Brit. Med. Jour.*, 1940, ii, 520.

The phenomena observed in acute pericarditis are practically identical with those in acute inflammation of other serous surfaces (pp. 16 and 22 *et seq.*), except for the fact that the arrangement of the fibrinous deposit is irregular, being modified ("churned up") to some degree by the constant movements of the heart. The exudate of serum into the sac may be so scanty that a "**dry**" or **fibrinous pericarditis** results. This form of pericarditis is seen especially in the inflammation which may supervene in cases of nephritis and pneumonia, but there is more usually a certain amount of effusion of fluid into the cavity. This effusion may be serous, sero-purulent, purulent or hæmorrhagic —its character depending to some extent on the nature of the causal agent. Thus, in a pericarditis due to the rupture of an abscess into the sac, or to direct invasion of pyogenic bacteria, the exudate is **sero-purulent** or **purulent.** **Hæmorrhagic** effusion may occur in nephritis, scurvy, purpura and hæmophilia, and also in tuberculosis and malignant growths of the pericardium or heart. In rheumatic cases, the exudate is **sero-fibrinous** in character or slightly turbid, but never definitely purulent. In pneumococcal pericarditis, the exudate may be fibrinous, sero-fibrinous or definitely purulent, the pus being thin and slimy. **Fibrin-formation** tends to occur in considerable amount in some cases, and both the peri- and epi-cardial serous layers become coated with whitish, shaggy masses of it, which, at first, are easily separated, but which, later, become vascularised and adherent. In its earlier stages, before such adhesions have taken place, this lesion has been described as the "honeycomb" or "dog's tongue" condition ("*cor villosum*"), and it has also been aptly compared to the appearance presented by pressing together and then drawing apart two thickly-buttered slices of bread (Fig. 9, p. 24).

In the early stages of the inflammation, the fibrin may form a very thin layer, and be present only at the base of the heart and around the origins of the great vessels. The causal organisms may be absent from, or difficult to find in, the exudate, but are present usually in the tissues at or near the surface.

Terminations of Acute Pericarditis. If the exudate is scanty, complete **absorption** may take place, but usually some of it persists and **organisation** of this produces, even at an early period, **adhesions** between the visceral and parietal layers. Dependent on the extent of the unabsorbed exudate, these adhesions may extend over the whole surface of the heart or may be limited in area. They are more liable to occur when there is little or no effused fluid to separate the inflamed surfaces, and at those parts of the heart which alter their relations to the parietal pericardium in least degree during cardiac movements, *e.g.*, near the apex, over the left auricle (atrium), and at the origin of the great vessels. Organisation of the fibrinous exudate may take place in localised areas over the epicardium, and thus may be formed the irregular, whitish areas of fibrous tissue, already described as one variety of **milk-spot** (p. 449). Sometimes portions of the fibrin remain unabsorbed, and **calcification** occurs in these, as well as in the adhesions and in the thickened patches on the surface of the heart or of the pericardium, forming at times a more or less complete **calcareous case.** Extension of the inflammation to more than the immediately subjacent superficial layer of the myocardium is not common, though extension to the neighbouring tissues of the mediastinum, pleura and chest-wall sometimes occurs. Dense fibrous adhesions between the myocardium, epi- and peri-cardium, and the adjacent and surrounding tissues of the mediastinum, pleuræ, and chest-wall may so hamper the action of the heart as to produce great **hypertrophy** of its walls and **dilatation** of its chambers (" *cor bovinum* "). Fatty degeneration may take place in the layers of cardiac muscle immediately subjacent to the inflamed epicardium.

Tuberculous Pericarditis is uncommon in man, though frequent in cattle. It may be secondary to tuberculous pleurisy or empyema, or to tuberculosis of the lung, mediastinal lymph-nodes, sternum or ribs. Miliary tubercles are rare in the pericardium, even as part of an acute and widespread general tuberculosis. A few scattered tubercles, usually along the coronary vessels, are sometimes seen in children. The epicardial surface is sometimes covered merely by a thin layer of fibrinous exudate indistinguishable from the non-tuberculous variety. On the other hand, the exudate in some instances is thick and irregular, and numerous adhesions may be present between the two serous surfaces. The exudate may be serous, purulent, caseous or hæmorrhagic. In some instances, the bacilli are found in large numbers in the fluid, but in the majority it is difficult to demonstrate them microscopically in the exudate. Usually, however, tubercle-granulations with giant-cells are seen, both in the organising fibrinous exudate and in the epicardium itself. Calcification may be a sequel to the tuberculous process.

Pneumopericardium. This is uncommon and is due to infection of the sac by one or more of the gas-producing organisms, *e.g.*, *Clostridium welchii*, *Clostridium œdematiens*, *Vibrion septique* (*Clostridium œdematis-maligni*), introduced usually through a perforating wound.

In compound fracture of the ribs or sternum and penetrating wounds of the chest, air may be introduced from without ; and, in gangrenous or tuberculous cavities in the lung, in pyo-pneumothorax, in ulceration of the œsophagus, and in subdiaphragmatic abscess, communication may be established between the lung or alimentary canal and the pericardial sac. In the majority of the cases the effusion becomes purulent.

Tumours. Fibromas and lipomas are found as primary tumours, but are extremely rare. Secondary tumours—lymphosarcomas, melanomas and carcinomas—occasionally occur. Of these, the carcinomas which arise from the bronchi (p. 569 *et seq.*, and Fig. 353, p. 575) are the most important. They extend by invasion from the lung, most frequently by way of invaded bronchial and mediastinal lymph-nodes or from other adjacent parts ; or they may be in the form of metastases from other organs. Secondary growths sometimes develop in the heart-wall and invade the pericardium. Epitheliomas have been recorded as arising secondarily to epitheliomas of the lip, tongue or œsophagus.

Parasites. Hydatid-cysts and cysticerci are occasionally present.

II. ENDOCARDIUM

The endocardium consists of a delicate layer of flattened endothelial cells which lie on a very thin supporting structure of fibrous tissue in which are a few elastic fibrils. The valve-segments or cusps are prolongations of the endocardium, with, at places, a slight amount of fibrous tissue and delicate elastic fibrils between the layers.

DEGENERATIONS :—

Cloudy swelling, fatty degeneration, amyloid degeneration and **calcification** occur, and are discussed on pp. 190, 194, 208 and 238.

In deficiency- and toxic diseases such as Addisonian anæmia, and phosphorus- or chloroform-poisoning, which give rise to fatty or other degenerative changes in the endothelium, minute hæmorrhages are found frequently in the endocardium immediately under the endothelium, especially that of the left ventricle. They are commonly associated with similar subepicardial hæmorrhages.

ENDOCARDITIS

For convenience this disease will be described under acute, subacute and chronic types, though the chronic is often a sequel of the acute variety, and acute and subacute exacerbations may occur in the course of the chronic disease. The main characteristic of the acute and subacute types is the formation of thrombi or vegetations upon the cusps of the valves, and in the chronic condition the development of fibrous tissue.

ACUTE ENDOCARDITIS

Although from the evidence available, we are not prepared to draw a strict line of distinction, on the one hand between rheumatic and non-rheumatic endocarditis : or between " simple " and " ulcerative " or " septic " endocarditis on the other, it is convenient for descriptive purposes to adopt some such classification. In many cases of " rheumatic " endocarditis, no bacteria are found in the vegetations, or on the cusps or even in the substance of the valves ; but, from other equally well-authenticated cases, many observers have isolated streptococci, and evidence has been obtained that the strains of streptococci thus isolated are, on inoculation intravenously into rabbits, capable of producing a non-suppurative, relapsing arthritis and endocarditis. Further, these streptococci may in one animal produce a " simple " vegetative endocarditis and in another an " ulcerative " form.[1]

I. **Rheumatic (Simple, Non-ulcerative) Type.** This, as the name would imply, occurs most commonly in acute rheumatism and allied conditions such as " rheumatic " chorea (p. 1072).

About 80 to 90 per cent. of the cases of this type of endocarditis are definitely rheumatic in origin, but a similar type has been described as associated with scarlet fever and other infectious diseases, and also as occurring during renal disease.

Morbid Anatomy and Histology. The valve-cusps especially are the sites of endocarditis, though in some instances there is a spread to the adjacent parts of the endocardium. During extra-uterine life, the valve-cusps of the left

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[1] " Acute Rheumatism caused by the *Diplococcus rheumaticus*," by J. M. Beattie, *Jour. Path. and Bact.*, 1904, **9**, 272.

side of the heart are affected more frequently than those of the right side, and the mitral more commonly than the aortic, though both of these valves may be attacked at the same time ; but it is rare to find a primary endocarditis affecting either the tricuspid or pulmonary valves alone. In intra-uterine life, the valves on the right side especially are attacked. This different liability, occurring in these two periods, is probably to be explained by the fact that the strain is greater on the right side during intra-uterine, and on the left side during extra-uterine, life, this strain rendering the cusps of the valves more vulnerable to attack. The affected cusps—which often have a slight pinkish tint from blood-staining—become swollen and translucent, especially at or near their free margins, which usually show an irregularly beaded appearance due to a deposit of blood-platelets on the roughened surface, such roughening being the result of swelling of and damage to the endothelial covering of the cusps. These **vegetations** are composed of masses of "conglutinated" platelets, and are at first papillary in character and resemble a delicate velvet-pile, later becoming increased in size by a further deposit of platelets. Leucocytes are entangled among these; fibrin is formed ; and the vegetations become enlarged, more opaque, and of a pale greyish-white or yellowish-white colour, in some instances attaining a considerable size. **Microscopically,** they are seen to be non-vascular homogeneous masses composed of fused blood-platelets and fibrin. At an early stage, in some cases, inflammatory œdema and proliferation of the cells immediately beneath the endothelium can be observed, this reaction having in all probability been the initial pathological lesion. On the mitral segments, the vegetations are almost invariably on the auricular (atrial) surface near the free margins ; and, on the aortic cusps, they are found most commonly on the ventricular aspect, at or near the edges of apposition, along the lunulæ, and on the corpora Arantii. If the inflammation is intense in the mitral segments, it may spread to the chordæ tendineæ, and even to the papillary muscles and neighbouring endocardium. These structures become swollen and infiltrated with inflammatory products, and the chordæ tendineæ sometimes rupture. From the aortic cusps, there may be a spread of the inflammatory processes to the wall of the ventricle, but this occurs chiefly in the septic type.

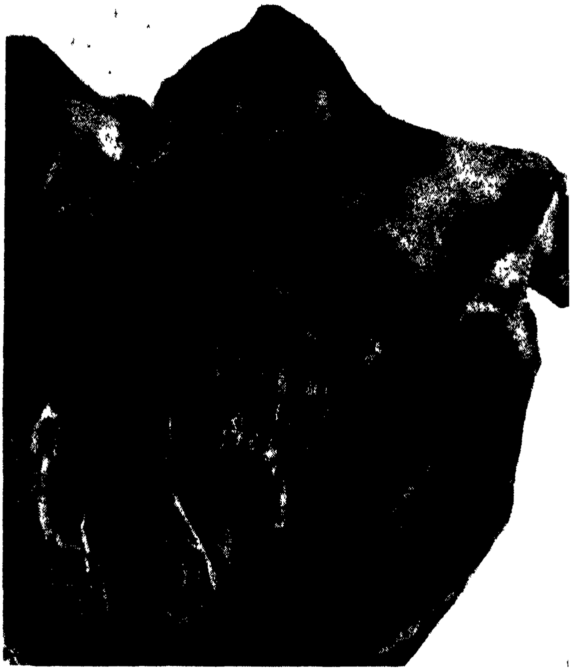

Fig. 252. *Simple acute (rheumatic) endocarditis.* Note the small vegetations at the base of the posterior cusp of the mitral valve. (The anterior cusp has been removed.)

Subsequent Changes in the Valves. If the inflammation is not severe and not prolonged, the reaction commonly subsides and the parts return to normal. More usually, however, there is some permanent damage to the valves, such as :—

i. **Adhesions,** which tend to form first at those parts of the valve where the segments are nearest to one another. The mitral valve-segments become adherent at the free lateral margins, between the adjacent chordæ tendineæ, and thus give rise to a funnel-shaped narrowing of the mitral orifice. At a later period, shrinking and fibrosis take place in the segments and the chordæ tendineæ become bunched together, thickened, shortened, and, it may be, adherent at places, producing a much diminished opening at the lower end of the funnel (Fig. 259, p. 458). On the other hand, the segments may become partially united on their adjacent surfaces in such a way that a slit-like or crescentic opening is formed—the so-called button-hole form of mitral stenosis (Fig. 262). One or other of these types of mitral stenosis is a common result of endocarditis, whereas incompetence of the valve-cusps, unassociated with stenosis, is a somewhat rare sequel. In the aortic valve, the adjacent cusps may become adherent to one another, producing stenosis of the orifice with or without accompanying incompetence.

FIG. 253. *Septic (or "malignant") endocarditis.* Note the large vegetations on the aortic valves and their extension to the mitral cusp.

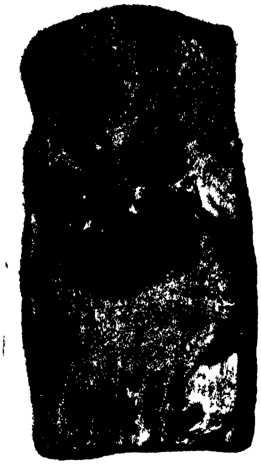

FIG. 254. *Acute septic endocarditis of aortic valve,* with extensive destruction and perforation of the cusps.

ii. **Contraction and thickening** of the valve-segments are common results of an acute endocarditis, for, during the inflammatory process, there is produced in the cusps a form of granulation-tissue which becomes organised and transformed into fibrous tissue. The thickening and contraction, thus produced, give rise to deformity of the cusps and consequent incompetence of the valves. This incompetence develops most frequently at the aortic orifice.

In the case of the auriculo-ventricular (atrio-ventricular) valve-segments, the fibrosis and contraction also as a rule come to involve the chordæ tendineæ and the papillary muscles.

iii. **Calcification.** After the inflammatory process has subsided, secondary degenerative changes are liable to occur and lime-salts may be deposited in the degenerated areas. This calcification causes rigidity, roughness, and irregularity of the cusps : produces incompetence and stenosis : and, on account of damage to the endothelium, leads to the formation of thrombi (vegetations) on the cusps. Such damaged cusps are apt to become the site of subsequent bacterial infection.

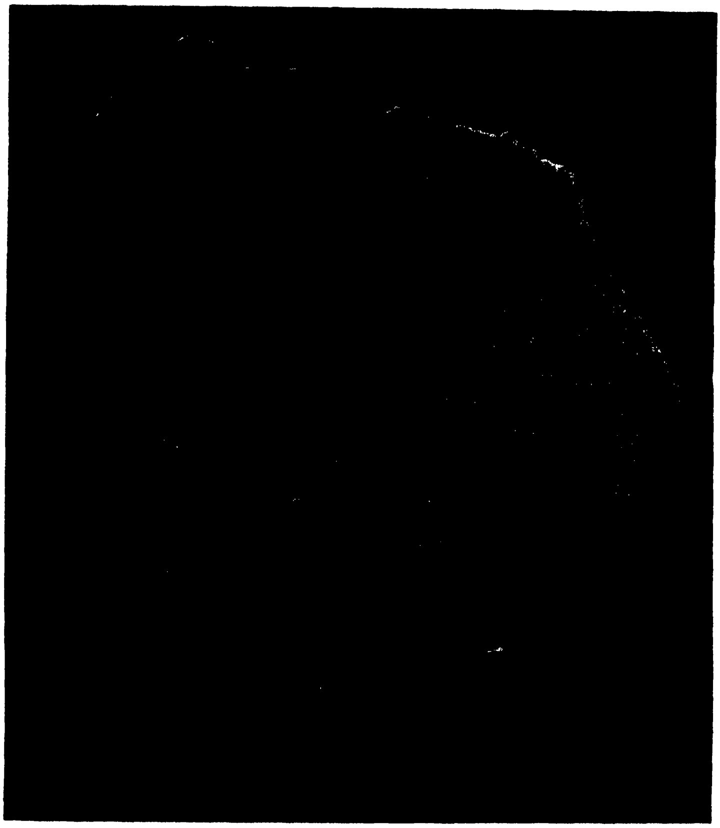

FIG. 255. (1) *Rupture of a previously diseased aortic cusp.* (2) Thickened cusp still in position. (3) Anterior cusp of mitral valve. Note the marked dilatation of the left ventricle. (Specimen lent by the late Professor Greenfield.)

II. **Septic (Bacterial, Ulcerative, or "Malignant") Type.** The most important organisms found in this type are *Streptococcus hæmolyticus*[1], *Staphylococcus aureus* and the *Pneumococcus* (*Diplococcus pneumoniæ*), but other organisms may be causal, and the endocarditis may be associated with arthritis, both the vegetations and the arthritis being then, in the majority of cases, due to the same organism, *e.g.*, pneumococcus, streptococcus or gonococcus.

Morbid Anatomy and Histology. The valves on the left side of the heart are attacked more commonly than those on the right in this type of the disease, but an involvement of the right side is more frequent than in the rheumatic form.

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[1] In an "Annotation" in the *Lancet* (1942, i, 83) on the classification of the hæmolytic streptococci, it is stated that : "Endocardial infection with group A streptococcus has in recent years been extremely rare, which throws into greater prominence these recorded infections with hæmolytic streptococci other than group A. The duration of infection may be short—two weeks—or as long as three to four months ; antecedent valvular damage is not usually present, and there is little or no response to sulphonamides. Cases infected by group B, the commonest group in the series of 11 (lettered groups) are characterised at autopsy by massive crumbling vegetations. In cases infected by G and C the vegetations may be flat, raised plaques or more bulky and friable, and there may be some association between the character of the vegetations and the fibrinolytic activity of the causal streptococci." (For the grouping of streptococci, *see* textbooks of bacteriology.)

The inflammatory reactions are more intense and more widely spread and the vegetations larger, much softer and more friable than in the rheumatic type of the disease. The vegetations frequently spread from the valves to the endocardium of the adjacent heart-wall—especially to any part coming in contact with the valves or vegetations upon them—and to the aorta. Ulcerative and other destructive changes are frequent both in the cusps of the valves and in the heart-wall, leading, it may be, to perforation of the cusps, and, in severe cases, to perforation of the wall of the ventricle at the membranous part of the septum, or of the aorta into the pulmonary artery where it adjoins the origin of the former vessel. Aneurysms of the cusps may be produced, and these, at a later period, may rupture, causing perforation. Such aneurysms are found especially on the mitral and aortic valve-segments. In the case of the mitral, they develop most usually upon the anterior flap, are directed upwards towards the auricle (atrium), and may perforate into it. On the aortic cusps, they are generally directed downwards, and perforate towards the ventricle. When such perforation has occurred, a ring of vegetations is usually found projecting from the surface around the orifice. Aneurysms are formed also in the wall of the aorta near its origin, or in the wall of the heart close to the commencement of that vessel, and these project towards the pulmonary artery or the right ventricle, into which they may open—though rupture into the pericardium is more usual. In some instances, rupture of the valves, or of the chordæ tendineæ, occurs ; and, especially where there has been long-standing endocarditis, the inflammation may spread for a considerable distance into the ventricular wall, and produce an extensive myocarditis. On account of the destructive changes which take place in the cusps, the softened and friable vegetations, or fragments of these, are easily detached, and may give rise to multiple emboli in the vessels of the spleen, kidney, brain, intestine, or heart, and produce in these organs such conditions as septic infarcts, abscesses, ulceration, or gangrene.

SUBACUTE ENDOCARDITIS or ENDOCARDITIS LENTA [1]

Under the term "**subacute bacterial**" or "**subacute infective endocarditis,**" a form which may be said to occupy a position midway between the rheumatic and the septic types is described. The onset is insidious, the condition arising most frequently in patients already suffering from cardiac disease—pre-existing valvular lesions, hitherto quiescent, becoming now the seat of a fresh infection. There is little doubt, however, that foci of chronic focal streptococcal infection in the teeth, tonsils, nasal sinuses, and elsewhere, are often sources of such re-infection. The fever and other initial symptoms resemble those of subacute rheumatism and the pre-existing valvular condition is commonly rheumatic in origin.

The heart is usually enlarged and the valves involved are the aortic and the mitral—the former more frequently than the latter. The vegetations, which are generally large and widespread, vary in appearance and consistence, and may be found, not only on the valve-segments, but also on the adjacent endocardial lining of the heart-wall. In old-standing cases, the vegetations become firm and even calcareous, but in the early stage they are soft and friable.

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[1] Latin *lentus*, slow or lingering.

FIG. 256 *Subacute bacterial endocarditis*, showing vegetations on both aortic and mitral valves

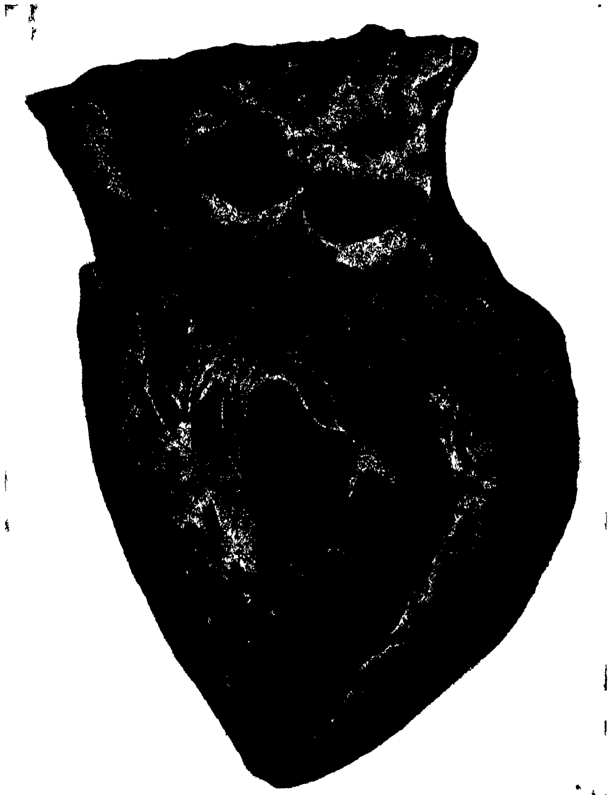

FIG. 257. *Subacute endocarditis*, with vegetations on the anterior cusp of the mitra valve and on the aortic valves.

Detachment of vegetations, with consequent embolic infarction in various organs, *e.g.*, brain, spleen, or kidney, is common. The petechial hæmorrhages in the skin, frequently seen in this condition, are due to the same cause. The spleen is often considerably enlarged, and infection of the kidney is usually of a focal character and is associated with hæmaturia (focal or embolic nephritis). The blood shows a secondary anæmia and a moderate degree of leucocytosis. The infecting organisms are usually streptococci of the salivary and fæcal types (*Streptococcus viridans* and *S. fæcalis*), but in some cases other bacteria are found. The organisms may be isolated from the blood by cultural methods. This type of endocarditis is characterised by its protracted course with clinical remissions, but also by its practically invariable fatal termination.[1] The commonest immediate causes of death are circulatory failure, uræmia and cerebral hæmorrhage, often with terminal pneumonic complications.

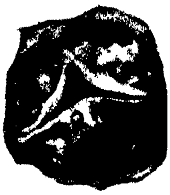

FIG. 258. *Chronic endocarditis of the aortic valve,* with nodular thickening and calcification, and showing adhesions between the cusps.

CHRONIC ENDOCARDITIS

In this condition, the affected parts of the valves are thickened and opaque; and sometimes, along the edges, firm, nodular projections are found. **On microscopical examination,** the cusps exhibit an increase of fibrous-tissue in which degenerative changes are seen, and which, by its contraction, has produced shrinking and perhaps puckering, and impairment of the function of the valves. In the degenerated areas, in the early stages, the subendothelial cells may show necrosis and fatty degeneration, whilst, at a later stage, lime-salts are deposited, and the valve-segments become much thickened, rigid, and even almost entirely calcified. The chordæ tendineæ, which often share in the process, become shortened and thickened. As a result of these changes, stenosis of the orifices and incompetence of the valve-segments may be produced.

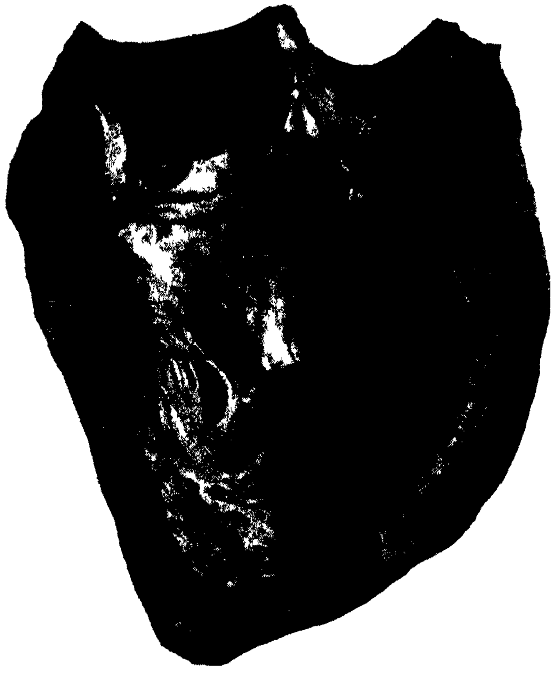

FIG. 259. *Chronic endocarditis of the aortic and mitral valves,* with shortening and adhesions of the chordæ tendineæ, and extreme stenosis of the orifice. There are small recent vegetations on the aortic cusps.

The aortic cusps are most frequently affected, and the condition is seen especially along their margins of contact—where the lunulæ join the bodies of the cusps and at or near the corpora Arantii—and along the attached borders. In the mitral valve, the changes are usually not so pronounced and are often more or less limited to the anterior curtain, especially towards its base near the left aortic cusp, at which part it is exposed to the strain, not only of the auriculo-ventricular (atrio-ventricular), but also of the ventriculo-arterial, blood-stream.

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[1] This statement will, we hope, with the use of modern chemotherapy, come to be modified in the near future.

Chronic endocarditis may be a sequel of acute endocarditis of any type, but supervenes most commonly in the rheumatic variety ; or it may be the end-result of a syphilitic infection of the cusps—usually the aortic—and is often associated with syphilitic aortitis involving the first part of the aorta. An analogous condition, but usually without adhesion of adjacent cusps to each other, may occur as a degenerative change—a chronic fibroid degeneration. This is seen in old age. It may occur also in chronic metabolic disorders or intoxications such as gout, chronic nephritis or nephrosis, chronic alcoholism and lead-poisoning. It is frequently associated with similar degenerative conditions in the blood-vessels.

VALVULAR DISEASE OF THE HEART[1]

Having studied endocarditis and the pathological changes produced by it in the various valves of the heart, it is convenient at this point to consider the effects produced on the heart itself, and also on the circulation, by those lesions which give rise to pure stenosis of an orifice and obstruction of the blood-flow, and to regurgitation which results from stenosis of the orifice or incompetence of the valve-segments. At the same time it must be remembered that the nutrition of the muscle of the heart is most important. During life, the muscle of the auricles, as a result of malnutrition and degeneration, may contract irregularly or " fibrillate," and so become inefficient as a regular propelling mechanism. The auricle is converted into a mere sac with quivering walls, and in this sac the blood accumulates. The ventricular muscle may also become weakened from associated myocardial lesions, or from circulatory stasis, may contract less effectively and thus undergo dilatation. The auricular fibrillation will necessarily lead to irregular ventricular contractions, and is frequently associated with mitral endocarditis or fibrosis of the cardiac muscle. (*See also under* " Heart-Block," pp. 474–5.)

1. THE MITRAL VALVE

(*a*) **Mitral Stenosis.** This is commonly the result of an attack, or series of attacks, of endocarditis, leading to adhesion of the valve-curtains to one another, and to narrowing of the orifice.

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[1] In following the descriptions of **disorders of the heart-valves,** our readers may find it helpful to refer to some of the illustrations of Cunningham's " *Text-book of Anatomy,*" 7th edition, 1937 —for example, Figs. 993 and 996—and it may interest them to learn that these and various other illustrations of Cunningham's "*Anatomy*" were the hitherto (and *still*) unacknowledged work of one of the authors, W. E. Carnegie Dickson, when a medical student in Edinburgh, and were originally prepared by him in association with Sir Harold (then Mr. H. J.) Stiles (at that time an Assistant in the University Department of Surgery), *not* for " *Cunningham,*" but for a joint "*Stereoscopic Atlas of Topographical and Applied Anatomy,*" and were, with that particular object in view, exhibited by Mr. Stiles and himself at the Annual Meeting of the British Medical Association held in Edinburgh in 1898 (see *British Medical Journal*, July 30th, 1898, page 335). Mr. Stiles was subsequently appointed Lecturer on Surgical Anatomy in the Anatomical Department ; and, a few years later, an " *Edinburgh Stereoscopic Atlas of Anatomy,*" " *prepared under the Control of the Department of Anatomy of the University of Edinburgh,*" was published by Dr. David Waterston, then Lecturer and Senior Demonstrator of Anatomy in that Department.

If the stenosis is extreme, and if there is no regurgitation, the left ventricle will become atrophied, owing to the reduced quantity of blood entering it, and, in consequence, its lessened need of functional activity in expulsion. The blood-pressure in the left auricle is raised, and the auricle, having to drive on its blood against a greater resistance, dilates and hypertrophies. It is lengthened in its vertical diameter, and assumes a somewhat conical shape; and its auricular appendage (auricle) is enlarged and elongated, and may extend round in front of the pulmonary artery, or even be doubled on itself like a horseshoe. Thrombosis may occur in the auricular appendage or in some other part of the auricle; and the endocardium of the chamber is thickened and shows an opaque-white, fibrous appearance. The increased resistance in the left auricle leads to venous congestion in the lungs, and the extra pressure thus produced in the pulmonary vessels acts upon the right side of the heart. The pulmonary artery and its branches are dilated and thickened, and may show a considerable degree of atheroma. The right ventricle undergoes dilatation and hypertrophy, assuming a quadrilateral shape, due in part to dilatation and thickening of the conus. The tricuspid valve, on account of the dilatation of the ventricle and the inability of its segments to close the orifice, may become incompetent. The right auricle, as a result, undergoes dilatation and hypertrophy; its endocardium is thickened, as is also that of the right ventricle, and thrombosis may occur in the auricle, especially in its appendage, which is also dilated and elongated. Obstruction to the systemic venous return into the right auricle is thus brought about, and the condition of chronic venous congestion occurs in the various organs and tissues.

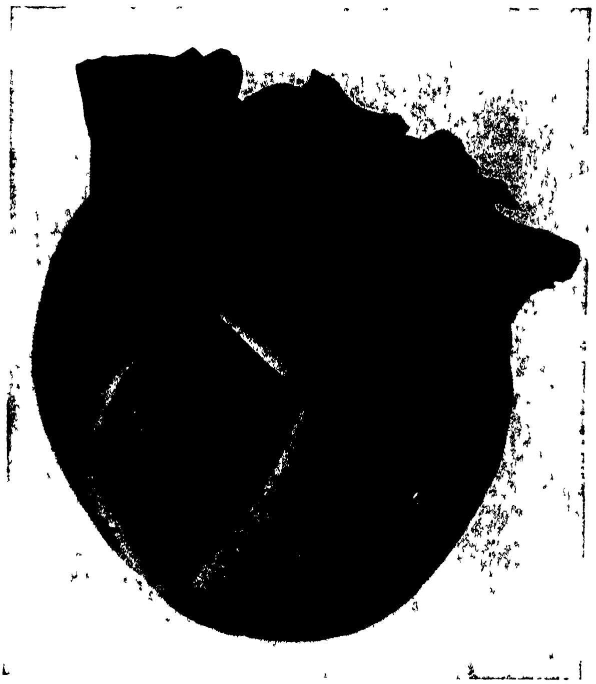

FIG. 260. *Great hypertrophy (combined with dilatation) of right ventricle* in mitral stenosis. Note the relatively small size of the left ventricle.

(*b*) **Mitral Incompetence** is due usually to long-standing endocarditis with a combination of retraction and contraction of the valve-segments, though it is also a sequel of dilatation of the left ventricle and the auriculo-ventricular (atrio-ventricular) orifice. As a consequence, the left auricle becomes dilated, and there may be some hypertrophy of it, but this is not an essential result of incompetence. The left ventricle undergoes dilatation and hypertrophy. The other chambers of the heart, as well as the lungs and other viscera, show changes almost identical with those seen in mitral stenosis.

In cases of mitral stenosis or mitral incompetence in which general chronic venous congestion is produced, the heart-muscle, especially of the right ventricle, is tough and indurated—a condition which is sometimes mistaken for interstitial myocarditis. The firmness is due in reality to an over-filling and distension of the blood-vessels, and a very similar physical state may be produced experimentally by injecting the coronary arteries with water. The condition is that of chronic venous congestion of the heart-muscle. (*See also* p. 150 *et passim.*)

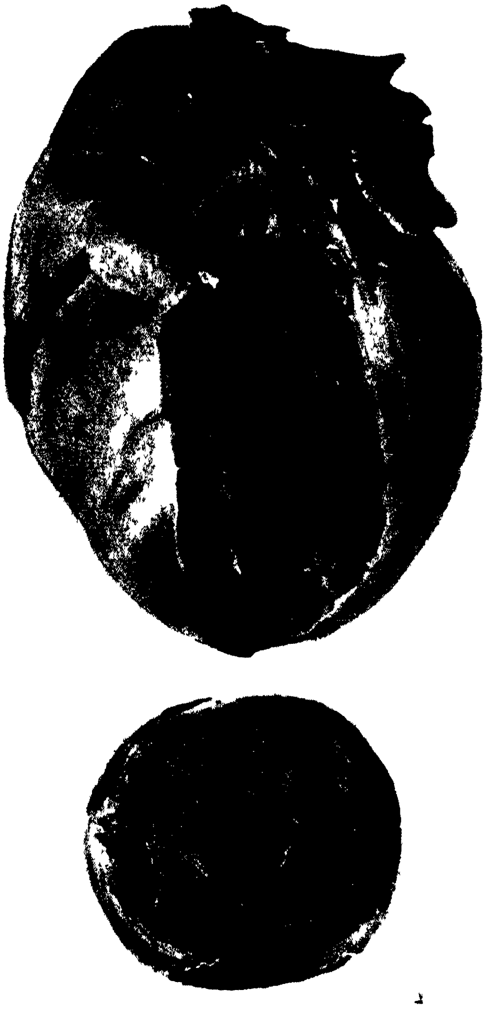

FIG. 261. *Hypertrophy and dilatation of left ventricle* in aortic disease. Below is a transverse section (near the apex of the ventricles) of a similar specimen showing "concentric" hypertrophy. Note also the crescentic cavity of the right ventricle (*see* p. 473).

2. THE AORTIC VALVE

(*a*) **Aortic Stenosis.** If adhesions between the cusps of the aortic valve are a sequel of the endocarditis, the aortic orifice will be reduced in diameter, and, if the propelling force of the left ventricle is proportionately increased, a gradual elongation of the ventricle and slowly-produced hypertrophic thickening of its muscular wall will occur. There may be little or no dilatation so long as the hypertrophy is sufficient to "compensate" for the increased resistance; but, if compensation fails, dilatation of the left ventricle also ensues, and, eventually, there arise conditions similar to those seen in cases of mitral incompetence.

(*b*) **Aortic Incompetence.** This may be produced by endocarditis (p. 452 *et seq.*), by degenerative changes in the cusps of the valve, or by their rupture—the latter the result usually of a violent strain, a crushing injury to the body, or a blow, especially if the cusps have been weakened by degenerative changes or by endocarditis (Figs. 254 to 257). It is commoner than stenosis, though the two conditions may be, and frequently are, associated. As a result of the incompetence, the left ventricle becomes hypertrophied, and, if the regurgitation of blood is considerable, the degree of dilatation may also be great. The dilatation, by widening of the auriculo-ventricular (atrio-ventricular) orifice, leads to secondary incompetence of the mitral valve, with all its resulting effects on the heart and other organs. In incompetence of the aortic valves, the coronary arteries are imperfectly filled, and the nutrition of the heart-wall suffers. The myocardium is not now able to respond to the extra strain thrown upon it, and still further dilatation of the various chambers follows.

3. THE TRICUSPID VALVE

(*a*) **Tricuspid Stenosis** may occur at any period of life, but is caused most commonly by endocarditis, either during intra-uterine or very early in extra-uterine life. The late Professor Greenfield was accustomed to state that stenosis of this orifice is almost constantly associated with mitral stenosis, and that the tricuspid orifice is never contracted to the same extent as the mitral. The results of this double stenosis are a vertical elongation of both auricles, dilatation of their cavities, hypertrophy of their walls, and an elongation of their appendages, which may almost meet on the anterior aspect of the heart. Usually, the ventricles are not much affected, though there is sometimes a slight amount of dilatation. The double stenosis, unless extreme, produces comparatively little effect on the general and pulmonary circulations, as the stenosis of the tricuspid orifice helps to balance the blood-flow on the two sides.

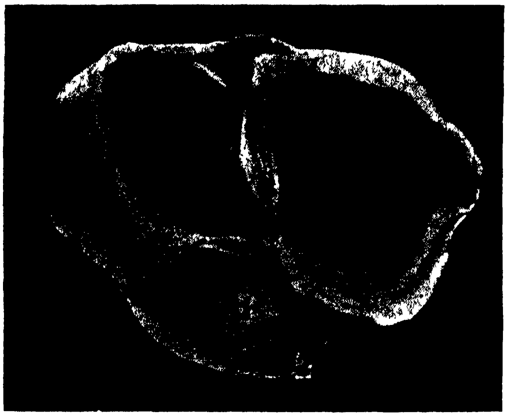

FIG. 262. *Mitral and tricuspid stenosis.*
1. Aorta. 2. Pulmonary artery. 3. Mitral orifice. 4. Tricuspid orifice.
(From a case of the late Professor W. S. Greenfield, R.I.E.)

(*b*) **Tricuspid Incompetence** may be produced by septic or ulcerative endocarditis; but by far the commonest cause is dilatation of the right ventricle, and, consequently, of the auriculo-ventricular orifice to such an extent that the valve-segments are unable to close it—complete closure being also prevented by the chordæ tendineæ, which are now of insufficient length. This incompetence may, as has been pointed out, be a result of the dilatation following mitral disease, but dilatation from any cause, *e.g.*, that following obstruction of the circulation through the lungs from local pulmonary disease, may produce it.

4. THE PULMONARY VALVE

(*a*) **Pulmonary Stenosis.** This may, if it originates during extra-uterine life, be the result of ulcerative endocarditis. Generally, however, the lesion is produced during intra-uterine life, and is caused by an attack of fœtal endocarditis, or may be the result of maldevelopment. If it occurs before the ventricular septum has been completely formed, the further growth of the septum may be arrested, and a permanent communication is thus established between the two ventricles (pp. 446–7) ; if at a later period, the chief effect is an extreme hypertrophy of the right ventricle. In such instances, the foramen ovale is found frequently to be patent. In some advanced cases, there is so much deviation of the septum between the aorta and the pulmonary artery that the aorta opens from both ventricles. Such multiple malformations of the heart may be of mutual advantage. This may be illustrated by the combination known as the "tetralogy of Fallot," which consists of (1) defect of the interventricular septum : (2) dextroposition of the aorta : (3) pulmonary stenosis : and (4) right ventricular hypertrophy. This combination is compatible with survival into adult life and is the commonest form of congenital heart-disease producing cyanosis in adults (*cf.* pp. 158–9 and 638).

(*b*) **Pulmonary Incompetence,** from disease or from tearing of the cusps by severe crushing injuries to the chest, is very rare.

THROMBI IN THE HEART

These may be divided into three main classes :—

1. Irregular **nodular** or **papilliform thrombi** or **vegetations,** which form on the valves, are described under endocarditis (p. 452 *et seq.*).

2. **Globular thrombi** are rounded or ovoid masses which are generally soft or even fluid in the centre. They vary in size, and may be so large as almost to fill a cavity of the heart. They are found mainly in dilated and hypertrophied chambers, where the blood-flow is impeded, or where eddies are formed. Thus, they are found at the apices of the ventricles, or entangled in the columnæ carneæ, and in the auricles where there is obstruction to the outflow of blood from narrowing of the valvular orifices. They lie free in the cavities (**Ball-thrombi**, Fig. 78, p. 164).

3. **Ante-mortem thrombosis,** the **formation of agony-thrombi,** and **post-mortem clotting** are discussed under Thrombosis (p. 161 *et seq.*).

III. MYOCARDIUM

INJURIES. *See under* "**Hæmopericardium,**" p. 448.

ATROPHY. In old age, the heart may be comparatively healthy and vigorous, atrophy being less common in it than in many other organs of the body. When it does occur, it may be the result of a slowly diminishing vascular supply because of arterial degeneration. Sometimes, however, it may have been preceded by hypertrophy, and, in such cases, the subsequent atrophy is more rapid in its course, and is due to the impaired nutrition of muscle already exhausted by the causes which had led to the hypertrophy. The period at which this exhaustion takes place varies, and is dependent, to a considerable extent, on the nutritive capacity and blood-supply of the heart-muscle. If the coronary arteries are degenerated, and the vascular supply of the heart is thus impaired, atrophy is liable to occur at an earlier stage. The wasting usually affects all the structures of the heart, the surface becomes wrinkled, and the arteries tortuous. The muscle assumes a dark-brownish colour—**pigmentary degeneration**—and the whole heart is atrophied, hence the name **brown atrophy** applied to this condition (pp. 220–1). On **microscopical examination,** the muscle-fibres are diminished in diameter, and an excessive amount of yellowish granular pigment may be seen in the cytoplasm round the nuclei especially towards their poles (Plate XI, Fig. 4, p. 222). The atrophy may be extreme, the heart being reduced, even to one-third of its normal weight. This condition is often well exemplified as a part of the general atrophy seen in wasting diseases, *e.g.*, cancer, diabetes mellitus, etc. In chronic pulmonary tuberculosis, atrophy of the heart is sometimes seen, but, in this disease, a common pathological finding is hypertrophy and dilatation, associated with the vascular obstruction in the lungs.

Atrophy may be localised to some special part or chamber of the heart as a result of loss of functional activity of that particular portion of the organ. Thus, in extreme degrees of mitral stenosis, the left ventricle receives a much reduced volume of blood through the narrowed orifice, and, in consequence, has its work correspondingly diminished, and may undergo considerable atrophy. Or again, especially in the right, but sometimes also in the left, ventricle, when the hypertrophy has lasted some time, a supervening atrophy of the papillary muscles and columnæ carneæ is a very constant feature, often accompanied by varying degrees of fibrosis.

DEGENERATIONS. Cloudy swelling and **fatty degeneration** of the heart-muscle are common and occur from the usual causes (pp. 190, 194 and 200).

Adiposity, or, as it is often called, **fatty infiltration** or **fatty loading** of the heart, is an abnormal increase of fat in situations in which it is commonly present in small amount, and a further infiltration of fat into the connective tissue lying between the muscle-bundles. As a consequence, atrophy of the muscle takes place, and first the superficial, and then the deeper, layers of the muscular wall are largely replaced by adipose tissue—the process occurring progressively from without inwards. In extreme cases, the fat even extends to and appears in patches immediately beneath the endocardium. This is usually best seen in the right ventricle, especially towards its apex, and in the

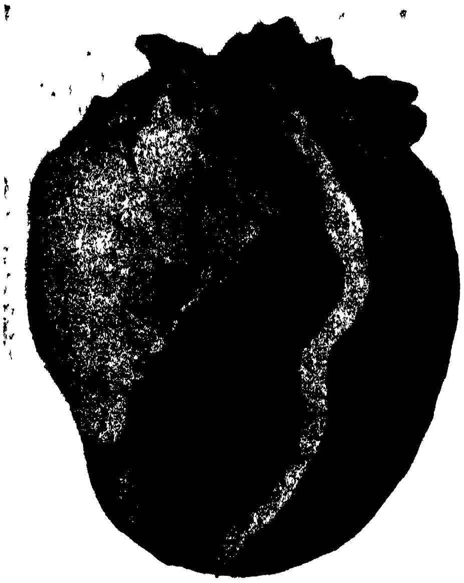

FIG. 263. Fatty infiltration of myocardium of right ventricle. Especially towards the septum and apex, the muscular fibres have been almost completely replaced by fat.

anterior wall near the ventricular septum, along the line of the coronary artery in that position (Fig. 263). It is also often pronounced in the ventricular wall just below the auriculo-ventricular groove. Varying degrees of infiltration may be found—from some slight increase in the amount of the subepicardial fat,

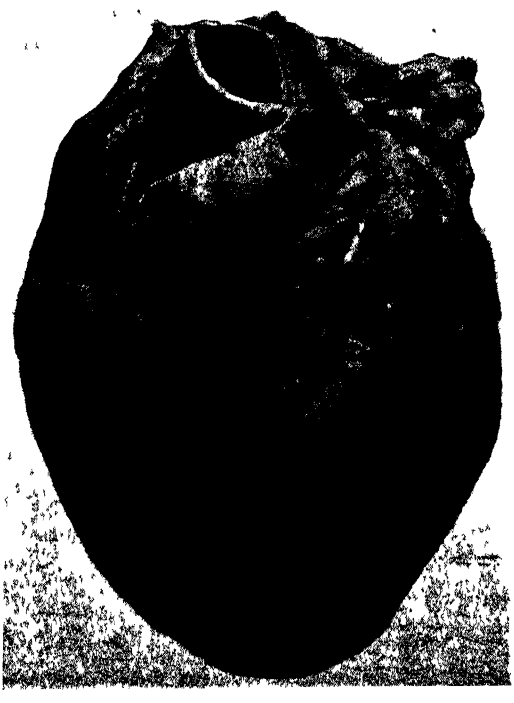

FIG. 264. Fatty infiltration of the heart showing excessive deposit of fat on its surface.

but without intermuscular invasion, up to conditions in which the line of demarcation between fat and muscle has become lost, and the entire muscular wall replaced, in certain areas, by adipose tissue. This adiposity of the heart may be merely part of a general obesity, but it sometimes occurs without any increase of adipose tissue elsewhere. Thus, it may be seen in old and debilitated persons, or in those suffering from some emaciating disease such as phthisis or cancer. It then is probably a sequel, rather than a cause, of the wasting of the muscle, and appears to be a process parallel with what occurs in voluntary muscle which has lost its function. One of the commonest causes of fatty infiltration of the heart is degeneration, thickening, and narrowing of the coronary arteries (*see below*). It is present in alcoholics, and is then often associated with atheroma.

Splitting of the muscle—where, microscopically, each fibre appears to be separated from its neighbour—is probably only a post-mortem artefact. Other degenerative changes—amyloid, hyaline and calcareous—occur, but are not common.

Death from immediately fatal systolic spasm can be caused by the injudicious injection of certain derivatives of camphor (*e.g.*, nikethamide) directly into the heart itself.

FIG. 265. Extensive atheroma of the aorta with ulceration and calcification. The heart-wall is thinned as a result of infarction due to narrowing and thrombosis of the corresponding branch of the coronary artery.

VASCULAR DERANGEMENTS :—

(*a*) **Chronic venous congestion** of the myocardium is common, and is associated especially with cardiac disease and with chronic venous congestion in other organs (p. 150).

(*b*) **Stenosis and Occlusion of Coronary Arteries and Coronary Thrombosis.** Though minute anastomosing channels exist between branches of these arteries, this anastomosis, from the point of view of function, is so imperfect that they may be regarded as end-arteries. They are peculiarly liable to degenerative changes, and are among the commonest sites of atheroma. The atheromatous changes may occur throughout the course of the artery, or may be confined to the opening from the aorta or to the first half-inch of the vessel. The results of these degenerative changes are narrowing of the artery, or partial or even complete obstruction of some of its branches, and serious interference with the nutrition of the heart-muscle. The muscle-cells show fatty degeneration and atrophy, and eventually many of them are replaced by fibrous tissue. These changes are usually patchy in distribution. Fatty infiltration is also a common sequel of such arterial disease. **Thrombosis** may occur in the degenerated vessels, producing complete obstruction. Blocking of the coronary arteries may also be caused by portions of clot or thrombi or vegetations which have become detached from their site of origin and carried as emboli into the arteries. If these emboli are septic, abscesses may be formed in the heart-muscle (p. 167 *et seq.*).

The effects of obstruction will vary according to the suddenness of the onset and the size of the obstructed vessel. Sudden obstruction of an important branch, however caused, will, if not immediately fatal, give rise to **infarction** in the heart-wall (*see* Infarction, p. 176). If the obstruction is only partial, the vascular degeneration leads to prolonged malnutrition of the heart, gradual degeneration and atrophy of the muscle-fibres and their replacement by fibrous tissue (fibroid heart). The amount of fibrous transformation will depend on the extent and degree of the vascular degeneration.

Microscopically, any residual necrotic and atrophied muscle-fibres become surrounded by, and enclosed in, fibrous tissue ; but ultimately nothing may remain but diffuse masses of such fibrous or scar-tissue.

Aneurysms of the Heart. Aneurysms of the heart are caused primarily by the degeneration of the muscle-fibres and their replacement by fibrous tissue (p. 176). This newly-formed fibrous tissue is relaxed and stretched at each diastole of the heart, but, being non-contractile, it is not shortened during systole ; and thus the contractile force of the rest of the muscle, being transmitted by the blood and acting upon this weakened area, gradually produces a distinct bulging of the affected portion of the heart-wall.

If the area of fibrous transformation is extensive, this aneurysmal bulging soon becomes pronounced, and gradually increases in size. Such aneurysms are more or less globular in shape (Figs. 266 and 267, p. 468), and are practically always confined to the left ventricle, especially to its anterior wall at or near the apex. More rarely, they may be found in the ventricular septum. A less common cause of aneurysm of the heart-wall is the extension of an aneurysmal dilatation in one of the segments of a valve, *e.g.*, the mitral, and secondary involvement of the wall of the heart. Thrombosis is common in the sac and rupture may cause hæmopericardium and death (p. 448).

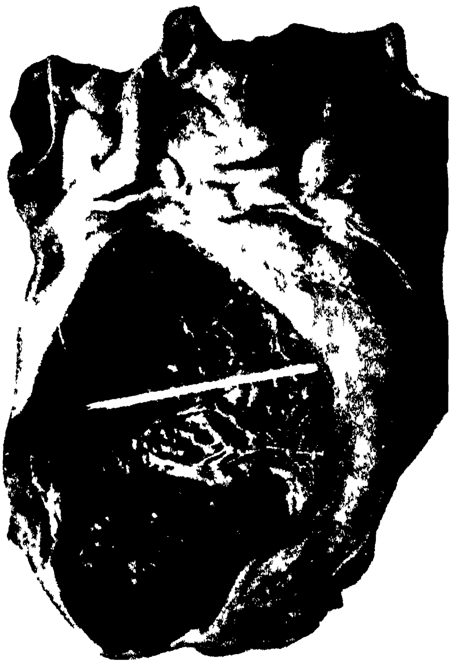

FIG. 266. Aneurysm of the heart, with thrombosis in the cavity of the aneurysm, which is situated in the septum near the apex.

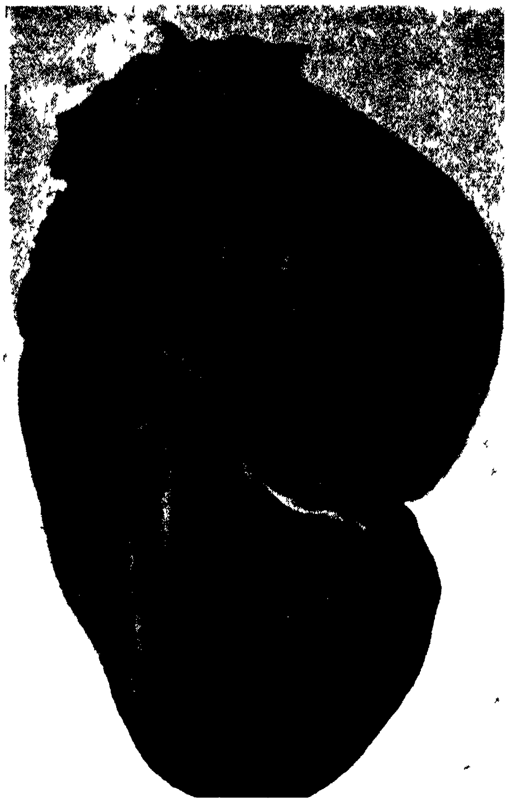

FIG. 267. Aneurysm of the heart—following coronary thrombosis. Note the presence of clot in the aneurysmal sac.

INFLAMMATION OF THE MYOCARDIUM :—

(*a*) **Acute non-suppurative myocarditis** arises generally by direct spread of the inflammatory process from the pericardium or from the endocardium. In the instances in which it follows acute pericarditis, the condition may be widespread ; whilst in those resulting from an endocarditis the lesion is usually localised. Acute myocarditis may occur during the course of an acute infective disease, *e.g.*, typhoid fever, diphtheria, scarlet fever or acute rheumatism. The lesions are usually produced by the toxins rather than by the bacteria themselves and are more of the nature of necrosis than of acute inflammation, are distributed irregularly, and, if occurring in the auriculo-ventricular bundle, may give rise to acute heart-block (p. 474). To the naked eye, the affected muscle-fibres are paler than normal, show a reddish mottled appearance, and minute, opaque necrotic patches may be seen ; but in many cases where, on microscopical examination, myocarditis is found, no naked-eye lesions are obvious. **On microscopical examination,** necrosis, cloudy swelling or other forms of degeneration are present, but the muscle-fibres become separated from one another by dilated and engorged capillaries, and by inflammatory exudate which is largely cellular in character. The cells may be of polymorphonuclear, or, more commonly, of lymphoid, type, and there may be also proliferation of the connective-tissue cells of the part. Hæmorrhages into and between the muscle-fibres are sometimes seen. Different infective agents may produce different types of reaction in the tissues and, therefore, the microscopical pictures may be somewhat dissimilar. For instance, the lesion produced by the toxin of diphtheria is predominantly a parenchymatous degenerative myocarditis; whilst that of typhoid fever is an exudative interstitial process, as well as a parenchymatous degeneration. Complete resolution may take place, but, usually, areas of necrosis and of immature or well-formed fibrous tissue remain as evidence of a former acute change These, however, though not, strictly speaking, "chronic" in nature, are more conveniently described under Chronic Myocarditis or Fibrosis (p. 470). The heart-chambers, especially the left ventricle, in the walls of which the myocarditis is present, frequently become dilated.

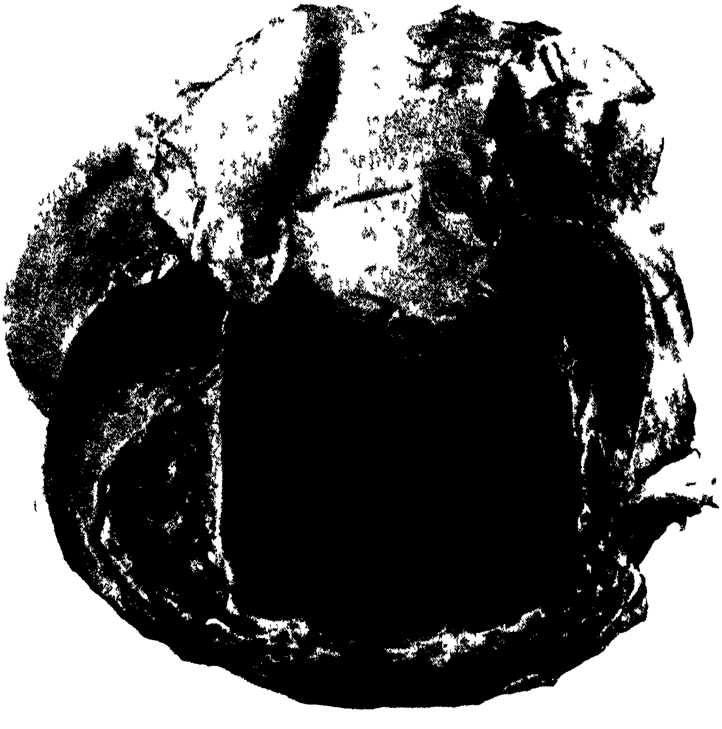

FIG. 268 Heart—coronary thrombosis Note thinning and fibrosis of muscle at the apex of the left ventricle, and the presence of a clot in an aneurysmal dilatation of the heart wall

(*b*) **Acute suppurative myocarditis** may be due to direct extension into the adjacent muscular wall of bacteria present in the vegetations of a septic endocarditis, or by the entrance of some of the crumbling vegetations into the coronary arteries; but it is associated most frequently with septic embolism of the coronary arteries, as part of a general pyæmic condition. It may occur in puerperal sepsis, but is perhaps commoner in acute periostitis or osteomyelitis. Abscesses, varying in number and in size, some of them microscopic, are formed in the heart-muscle, especially of the left ventricle near its base and anterior surface. These abscesses are surrounded by a *zone of congestion*, and hæmorrhage may take place into or around them. **On microscopical examination,** fatty and necrotic changes are seen in the muscle-fibres, and collections of various forms of leucocytes, and sometimes the causal bacteria, are found in and between the fibres. If the abscesses are near the surface of the heart, they may rupture into the pericardium and give rise to suppurative pericarditis; or they may burst inwards through the endocardium.

(*c*) **Chronic Myocarditis—Fibrosis.** In this lesion, there is overgrowth of the fibrous tissue, not only between the muscle-bundles, but also replacing the degenerated and atrophied muscle-fibres themselves. This new formation of fibrous tissue interferes with the nutrition and causes further atrophy of the muscle, and thus fibrous patches of varying size, either localised, or scattered irregularly throughout the myocardium, are produced. This condition is found most commonly in the anterior wall of the left ventricle near the apex, in the septum, in the tips of the papillary muscles, and in the columnæ carneæ. The newly-formed tissue may be cellular and show only masses of lymphocyte-like cells and proliferated connective-tissue cells; but, as a rule, it consists of well-organised and fully developed fibrous tissue. This fibrous transformation of the myocardium is often described as "**fibroid heart**" or "**fibroid degeneration of the heart,**" but, under these terms, are included various types of fibrosis, similar in character, though due to different causes. The principal of these are :—

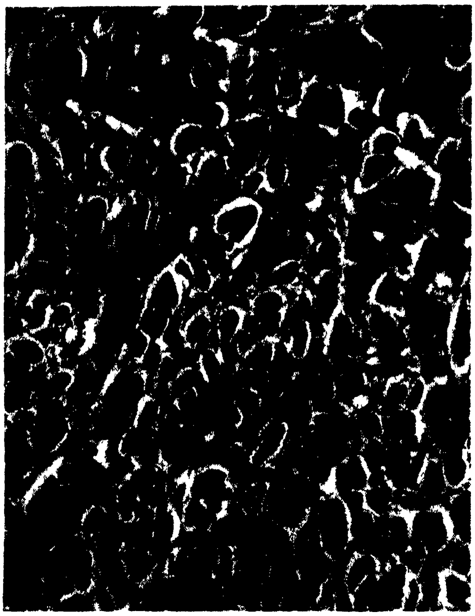

FIG. 269. Low power of muscle of left ventricle, showing diffuse interstitial myocarditis. Mallory's connective-tissue stain. × 100.

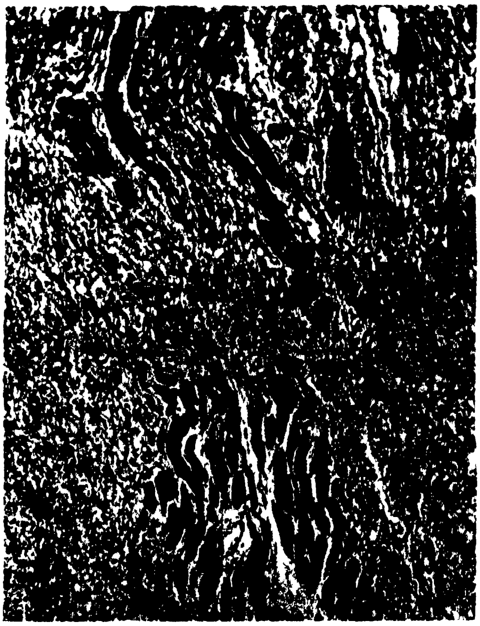

FIG. 270. Interstitial myocarditis. The muscle-fibres have, in large part, disappeared, and have been replaced by a moderately cellular connective tissue. Hæmatoxylin and eosin. × 75.

i. That form of fibrous-tissue overgrowth which is dependent upon degenerative changes in, or obstruction of, the coronary arteries. Thus, after infarction of the heart (p. 176), there may be replacement of the necrotic muscle-fibres by fibrous tissue, which is in reality scar-tissue. More commonly, however, the fibrous transformation in the myocardium is a purely degenerative process resulting from an impaired blood-supply and consequent malnutrition. the more highly-functioning muscle-fibres degenerating and being replaced by the less specialised fibrous tissue. Microscopical examination shows that the fibrous tissue is irregularly scattered, and para-arterial in its distribution—*i.e.*, it is not immediately round the vessels but in their neighbourhood. The peri-arterial muscle-fibres are intact, and little islets of muscle, often showing degenerative changes, are seen embedded in the fibrous tissue. The fibrous tissue adjacent to the muscle is often highly cellular, while that farthest away has a hyaline appearance.

ii. A purely degenerative change, seen chiefly in old age in those cases where vascular degeneration is not prominent. In such conditions, the papillary muscles and the columnæ carneæ of the left ventricle are the principal, and may be the only, parts affected. This is not uncommon in wasting diseases—even in children. A similar picture is seen as a consequence of long-standing hypertrophy and dilatation of the right ventricle.

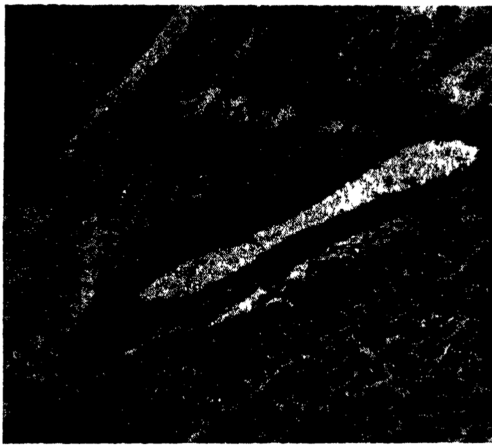

FIG. 271. "Aschoff-body" in a late stage, showing a well-developed fibrocellular zone surrounding a blood-vessel. × 90.

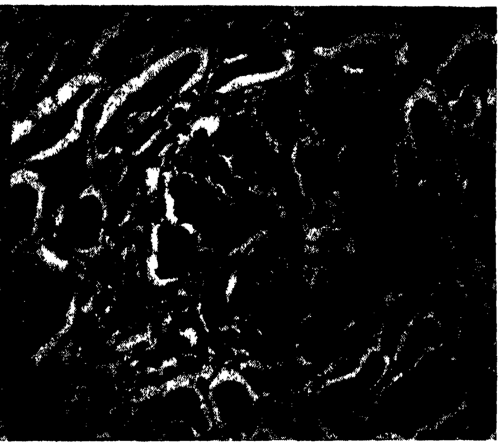

FIG. 272. "Aschoff body" in the wall of the heart. Hæmatoxylin and eosin. × 400.

iii. Interstitial overgrowth which is mainly a sequel of rheumatic myocarditis, the result of the ordinary processes of repair, and characterised by the presence of minute or "submiliary" nodules and zones of leucocyte-infiltration. The foci are rounded or fusiform, and are composed of large elongated or rounded cells, lying in the intermuscular connective-tissue trabeculæ. The nuclei of the cells are often multiple and do not stain intensely, though their cytoplasm stains deeply and uniformly. These large cells lie loosely-packed in a fine fibrillary matrix composed of fibrin, and, surrounding them, are found leucocytes chiefly of the mononuclear type. These "**Aschoff's nodules**" appear to arise from the peri-arterial connective tissue, or from the tunica adventitia of the artery itself. They are found both in the sub-epicardial tissues and in the deeper parts of the myocardium, particularly in the wall of the left ventricle at the origin of the aorta, at the apex close to the septum, and at the attached margins of the segments of the mitral valve. They are less abundant in the right ventricle and in the ventricular septum, and are comparatively rare in the auricular walls. These nodules appear to be stages in the production of a scattered myocarditis, which, at a later period, is demonstrable in the form of irregular fibrous nodules or cicatrices. That these nodules are specific of acute rheumatism, as suggested by Aschoff and Coombs, is generally accepted, but some observers have failed to find them in definitely rheumatic cases, or, at all events, cases which have all the other features of rheumatic fever. Leucocyte-infiltration, lymphocytic in character, *is* found in the myocardium in the majority of infective diseases, including acute rheumatism, but the nodules so produced are small and, so far as our experience goes, they do not correspond with the submiliary nodules described by Aschoff.

Peri-arterial fibrous increase is almost always associated with a varying amount of similar fibrosis of para-arterial type.

iv. **Tuberculous Myocarditis** is described on p. 76 : **Syphilitic Myocarditis** on pp. 87–8.

HYPERTROPHY AND DILATATION :—

Hypertrophy and **dilatation** of the heart are conditions which are frequently associated with one another. The hypertrophy of the muscular substance is, in many cases, compensatory, and occurs because of some extra strain thrown on the heart (p. 264). The same cause may give rise to dilatation, and, in some cases, it would seem as if the dilatation were primary, and that the hypertrophy were the consequence. Frequently, however, the dilatation is a sequel of muscle-exhaustion in a hypertrophied heart. This intimate connection makes it convenient to study them together.

Ætiology. Apart from the effects of valvular lesions in producing hypertrophy and dilatation of the heart (pp. 459 to 463), there are many other causes, some of which act on the heart as a whole, whilst others act on individual chambers.

1. **On the heart as a whole.** Adhesions, not only between the epi- and peri-cardium, but also between the pericardium and the pleura or chest-wall, cause the heart to work under considerable difficulties, and are, therefore, one of the most certain causes of hypertrophy, some of the largest hearts on record ("*cor bovinum,*" p. 451) having so resulted. The adhesions are the sequel of pericarditis, with or without mediastinitis and pleurisy ; and, in some cases, the pericarditis is associated with valvular disease.

Minor degrees of hypertrophy are produced by prolonged over-stimulation of the heart, and the enlargement of the heart during pregnancy is probably to be explained on the ground of temporary extra strain. Excessive muscular exercise also leads to hypertrophy, and is common in athletes and in those doing heavy muscular work. Very frequently, this general hypertrophy is associated with dilatation, and the relative degrees of hypertrophy and dilatation will depend, to a certain extent, on the previous state of nutrition of the heart-muscle. If the muscle is degenerated, dilatation, rather than hypertrophy, will be the result of overstrain ; whereas, in healthy muscle, if the strain is gradually applied, hypertrophy is the common result.

2. **Localised to one or more chambers.** This is very common, and may be associated especially with diseases of the kidney, with valvular diseases of the heart, and with diseases of the arteries, lungs and pleura. In chronic nephritis, the left ventricle especially is affected, and the hypertrophy is probably due mainly to the increased arterial tension resulting from the non-elimination by the diseased kidneys of products, normal and abnormal, and the retention of these in the circulating blood, the heart having to drive the blood through the tonically contracted peripheral arterioles. The hypertrophy may occur rapidly, *e.g.*, in from eight to twelve weeks. The condition is generally a pure **concentric hypertrophy**, unaccompanied by dilatation (Fig. 261, p. 461). There is, owing to the continuity and arrangement of the muscular fibres and to overworking of the whole heart, usually some associated hypertrophy—frequently with considerable dilatation—of the right side.

Chronic degenerative and other forms of arterial disease, and especially the diffuse form of arteriosclerosis, by causing the narrowing of the lumen of the arteries, increase the work of the left ventricle, and therefore tend to produce hypertrophy of its muscular wall.

Diseases of the lungs such as emphysema, interstitial pneumonia of any variety, or diseases of the pleura, as, for example, pleural adhesions, may give rise to hypertrophy of the muscular wall of the right ventricle (Fig. 260, p. 460). This hypertrophy is commonly associated with dilatation.

Hypertrophy and dilatation affecting the auricles alone are almost always the result of cardiac valvular disease.

Pathological Anatomy. In general hypertrophy of the heart, there is enlargement of all the chambers, and the normal shape is not much altered. When the left ventricle in particular is affected, the organ is increased in length and is more pointed than normal. The apex extends further to the left. On section, the walls of the ventricle and the septum are found to be increased in thickness, the septum often bulging into the right ventricle. This is well seen in transverse section (Fig. 261 p. 461), the chamber of the right ventricle, in such a section, often appearing as a crescentic slit-like opening. Microscopically, there is an increase in size, as well as in the number, of the individual muscle-fibres. When the right ventricle is hypertrophied, the organ assumes a more quadrilateral shape, its apex is obtuse, and the transverse measurement increased (Fig. 260, p. 460). The right ventricle comes to occupy almost the whole of the anterior aspect of the heart. On section, the wall is hypertrophied and the cavity usually dilated.

GRANULOMATA :—

Tuberculosis is rare (pp. 76 and 451).

Syphilitic gummata in their relation to heart-block are referred to on p. 474.

NEW GROWTHS. Primary tumours are rare, but sarcomas, fibromas, lipomas, myxomas and myomas, both in the muscle and on the valves, have been recorded. The congenital rhabdomyomas which are found in the myocardium are described under Tumours (Fig. 149 and pp. 314–15). They are found especially in certain cases of congenital idiocy, associated with tuberous sclerosis of the brain, adenoma sebaceum, and congenital tumours of the kidneys and other organs (p. 1134).[1]

Secondary growths of melanotic sarcomas, lymphosarcomas, and carcinomas may occur. Invasion of the pericardium and the heart by bronchial carcinoma is not uncommon (Fig. 353, p. 575).

Hydatid-cysts (p. 400 *et seq.*) have been found in the heart-wall.

HEART-BLOCK :—

Anatomical and histological investigation has shown that, in various regions of the heart-wall, peculiar systems of muscular fibres exist. These are regarded as remains of the primitive musculature, and Keith holds that the greater part of the tissues of the auricles (atria) and of the ventricles are outgrowths from the primitive cardiac tube, and that, in the auricle, the subsequently-developed muscular tissue has spread over the primitive remains, covering or displacing them. Portions of this primitive tissue, in isolated masses, are found at the junction of the right auricle with the superior vena cava (the sino-auricular (S-A.) node), in the vicinity of the coronary sinus and elsewhere. The muscle-tissue joining the auricles and ventricles (the A-V. bundle) probably belongs to the same system. The sino-auricular node lies at the junction of the free border of the right auricular appendage with the superior caval termination. The muscular fibres are small, being about one-half or one-third the breadth of those of the auricular fibres proper. They are striated, fusiform in shape, are embedded in dense connective tissue and contain a few ganglion-cells, nerve-plexuses and blood-vessels. The auriculo-ventricular node lies at the posterior and right border of the ventricular septum just above the coronary sinus and close to both the tricuspid and mitral valves—so close indeed that pathological lesions of these valves may spread to this node. The generally-accepted view is that the impulse to cardiac contraction starts at the sino-auricular node into which the fibres of the vagus and sympathetic nerves enter, and passes by way of the ordinary muscle-fibres to the auriculo-ventricular node and then to the muscle-fibres of the ventricles through the auriculo-ventricular bundle and its arborisations. This bundle, arising at the node, passes to the membranous part of the ventricular septum and there divides into right and left branches. Both branches split up into numerous sub-branches, and it is by way of this arborisation that direct communication with the ventricular muscle-fibres is effected.

Thus it happens that pathological states affecting either the nodes or the connecting-bundles will cause disturbance in the conductivity of the heart-muscle, with the production of, it may be, complete or partial heart-block, fibrillation, auricular flutter and tachycardia. Post-mortem examination of the hearts from such cases may show that the nodes or the conducting fibres are invaded and destroyed or interrupted by syphilitic gummata, fibrosis or necrosis with or without calcification, ulceration, parenchymatous or fatty degeneration: or changes such as diffuse fibrosis, calcification, lymphocytic infiltration and other chronic inflammatory processes which have originated in the mitral valve and spread to the auriculo-ventricular node and bundle. Thus the results of occlusion of the coronary artery, syphilis, rheumatism, diphtheria and typhoid fever may cause heart-block. Interference with conductivity, producing tachycardia and auricular flutter, has been described in connection with exophthalmic goitre, so-called "functional" nervous diseases, etc. These clinical symptoms and the occurrence of actual heart-block are recorded in cases in which no obvious pathological lesion has been detected, but, as the lesion may be very small, only a negative finding in complete serial sections could be assumed as proving its absence. Those of our readers who wish to supplement this brief summary of the important subject of heart-block should refer to the fuller accounts of it to be found in special articles and in works on clinical medicine and cardiology.

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[1] *See* footnote, p. 1134.

SECTION III

DISEASES OF BLOOD-VESSELS

In the study of arterial disease, it is important to remember that, even in otherwise apparently healthy people, degenerative changes in arteries are liable to supervene as age advances. The muscular tone and elasticity are gradually reduced, atrophy of the muscular and elastic fibres takes place, new fibrous tissue is formed and lime-salts may be deposited in the vessel-walls. These changes produce greater rigidity in the vessels and often lead to dilatation. The degenerative changes are intensified by diseases which cause variations in blood-pressure and increased strain. The arterial blood-pressure is controlled by the output of blood from the heart, the peripheral resistance and to a less extent by the elasticity and resilience of the large arteries. The volume of the cardiac output depends on the force and rate of contraction of the heart, and the size of its chambers, especially the left ventricle—the peripheral resistance on the contractility of the arterioles, especially of the splanchnic area and the skin, and in a minor degree on that of the capillaries. The contraction and dilatation of these vessels, is, in part, under the control of the vasomotor centre—the impulses arising in the hypothalamic nuclei being transmitted through the autonomic (sympathetic and parasympathetic) system. Therefore, in explaining variations in blood-pressure it is not sufficient to picture merely obvious pathological lesions in the arterial walls. Though the nutrition of the wall of the vessel is of the utmost importance, changes in the hypothalamic nuclei and in the fibres conducting nervous impulses should also be considered. In the smaller and medium-sized vessels, resistance to strain depends mainly on the muscular coat; but, in the larger vessels, the presence of more elastic tissue in their walls increases their resiliency and power of resisting dilatation. Anything, therefore, interfering with the nutrition of the muscular and elastic tissue will cause variations in blood-pressure and increase the tendency to degenerative changes. Again, the nutrition of the vessel depends—perhaps in greater degree than does that of any other organ or tissue—upon the condition of the blood flowing through it, the inner coat being nourished mainly by the blood with which it is in contact. An impoverished condition of the blood, including any deficiencies in the necessary vitamins (Chapter XV, p. 439), or the presence in it of toxic and irritating substances, will act with special severity on the endothelial lining and possibly other parts of the wall of the arteries. Experiment seems to show that certain toxic substances, when present in the blood, produce thickening of the inner coat of the vessel, whilst others act especially by causing degenerative changes in the media. If the inner coat becomes much thickened, interference with nutrition in the layers adjacent to the internal elastic lamina follows, and degenerative changes are liable to occur. Toxic substances, bacterial or chemical: endocrine effects and especially the action of adrenaline: certain "pressor" substances ("renin" and "angiotonin") produced by the kidney, in both normal and abnormal circumstances, especially by the "ischæmic kidney" (pp. 492 and 869); and possibly other factors of which we know little, may act by causing spasm or dilatation of the vessels: or by altering the "selective" capacity of, or by bringing about degenerative changes in, the endothelium and the other coats of the vessels. Efficient nerve-control of the vessels is essential to a healthy condition of their walls (*see under* "Raynaud's Syndrome," pp. 167, 187, 244, 483 and Figs. 764 to 768, pp. 1193 to 1197).

I. THE ARTERIES

Arteries can be divided into three classes—**arterioles,** *e.g.*, afferent arterioles of the kidney: **medium-sized,** such as the radial or femoral: **larger,** *e.g.*, the aorta. The lumen of each is lined by flattened endothelial cells, subjacent or external to which are elastic fibres forming an internal elastic lamina which is very thin in the arterioles: more definite in the medium-sized vessels, in which additional layers of interlacing elastic fibres and thin collagenous bundles are developed between the endothelium and the internal elastic lamina. This additional tissue becomes more definite and abundant with the increase in calibre of the individual arteries: and, in the aorta, is composed of several lamellæ of longitudinal, interlacing elastic fibres, a few collagenous fibres and some smooth muscle-cells.

The tunica media consists of smooth muscle-fibres which encircle the tube in a single, several, or many, layers, according to the size of the artery. Elastic fibres are present between these muscular layers in the medium-sized vessels ; and, in the aorta, the media consists mainly of elastic fibres. In the arterioles, the adventitia consists of loose connective tissue with a few elastic fibres ; in the medium-sized arteries, the elastic fibres are more numerous and form an external elastic lamina immediately adjacent to the outer aspect of the media ; in the larger arteries, the adventitia is relatively thin, similar in structure to that of the medium-sized arteries, but not so sharply marked off from the media. Where the smaller arteries merge into capillaries, the internal elastic lamina becomes progressively thinner until it disappears.

Blood-Supply. The commonly-accepted view is that the adventitia and the media are supplied from vasa vasorum, but that the intima receives its nourishment from the blood circulating through the lumen. Winternitz [1] and his co-workers (1938) have shown that, in the larger and medium-sized arteries at all events, the intima has a network of small vessels anastomosing with those of the media and adventitia and giving off fine ramifications just beneath the endothelium. They also maintain that vasa vasorum may arise from the lumen of the artery itself (*see* also p. 491).

For further details on the structure of arteries readers are referred to Schafer's "Essentials of Histology," 14th ed., edited by H. M. Carleton, 1938.

INJURIES. Apart from the damage which may take place to any artery in an open wound, bruising may be followed by circumscribed hæmatomas, or even aneurysmal dilatations, without rupture or puncture of the vessel.

ATROPHY may follow loss of function, as, for example, in the arteries of the proximal part of a limb after amputation, or in the arteries supplying glandular structures which have undergone involution.

HYPERTROPHY. After obstruction of an artery, if collateral circulation is established, an actual growth of all the structures in the walls of the collaterals takes place. This is a compensatory mechanism. A consideration of the unequal and irregular strains to which the heart and the arteries are subjected, even in normal individuals, will make evident the value of this capacity for adaptation and compensation. If the vessels, in their normal condition, cannot bear the strain of a further increase in blood-pressure, dilatation and thinning of their walls will follow. To prevent these phenomena from occurring, hypertrophy and hyperplasia of the muscular and elastic fibres take place. In disease, these proliferative changes are seen in cases of high blood-pressure due to involvement of the kidney, and in some of these there is no evidence of primary arterial disease. The few muscle-cells which are normally present in the intima and which lie parallel to the long axis of the vessel and on the inner aspect of the internal elastic lamina, undergo increase, sometimes to a considerable extent. Increase of elastic tissue in all the coats is also a feature. It is true that, with continued pressure, other changes develop ; the hypertrophied muscular and elastic elements fail and are replaced by fibrous tissue both in the middle and outer coats ; and the inner coat becomes thickened by fibrous-tissue overgrowth in its subendothelial layer. The presence of this new tissue lessens the contractile power of the artery, but makes its wall more resistant to dilatation from increased blood-pressure.

DEGENERATIVE CHANGES. Fatty, amyloid and hyaline changes occur in arteries and are referred to in Chapter VIII, pp. 201, 212 and 214.

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[1] "The Biology of Arteriosclerosis," by M. C. Winternitz, R. M. Thomas and P. M. le Compt, Yale Medical School. Published by Charles C. Thomas, Baltimore, 1938.

INFLAMMATORY AND PROLIFERATIVE CHANGES.

These may be classified as follows :—

1. **Acute Arteritis.**
   (Including polyarteritis acuta nodosa.)
2. **Proliferative Arteritis.**
   - (i) Syphilitic disease.
   - (ii) Tuberculous disease.
   - (iii) Endarteritis obliterans.
     - (*a*) Ayerza's disease.
     - (*b*) Thrombo-angiitis obliterans.
   - (iv) Rheumatic lesions.
3. **Chronic Arteritis.**
   - (i) Calcification.
   - (ii) Atheroma.
     - (*a*) Nodular.
     - (*b*) Diffuse type affecting larger vessels.
   - (iii) Arteriosclerosis.

1. **ACUTE ARTERITIS.** Arteries are liable to share in any acute inflammatory changes which occur in their neighbourhood, but a primary acute arteritis, as an isolated and independent lesion, is rare and is confined almost exclusively to the inner coat of the large blood-vessels, particularly the aorta near its commencement. The disease may arise as an extension of acute endocarditis of either the aortic or pulmonary valves ; and it is said to occur as a result of severe syphilis, especially if associated with excessive alcoholism. In any type of acute arteritis, thrombosis is a common complication. If sepsis is present, the infected thrombus undergoes softening, and the septic emboli perhaps become impacted in the smaller arteries, producing acute inflammatory and suppurative lesions in and around the vessels. Multiple acute aneurysms may develop as a result of the damage to the walls of the vessels.

Microscopically, the walls are seen to be infiltrated with leucocytes, the connective-tissue cells between the laminæ of the inner coat swollen and proliferating, and the muscle-fibres often necrotic and separated by inflammatory exudate and, it may be, undergoing necrotic changes. In the suppurative forms, abscesses are sometimes found round the blocked and infected vessel.

Polyarteritis Acuta Nodosa is a rare disease, the first case in this country having been described by Carnegie Dickson.[1] It occurs mostly in males, and is characterised by the formation of small localised nodules upon the smaller and medium-sized arteries. These nodules show local inflammatory changes, such as infiltration of the adventitia with leucocytes and other inflammatory products, necrosis of the vessel-wall (especially of the media), usually with the formation of a small aneurysm, and thrombosis of the contents of the lumen and of its aneurysmal dilatation. There is, in addition, rupture of the internal elastic lamina and often considerable thickening of the intima.

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[1] "Polyarteritis Acuta Nodosa and Periarteritis," by Carnegie Dickson, *Jour. Path. and Bact.*, 1907, **12**, 31. "Panarteritis acuta nodosa" might be considered a more appropriate term for the condition.

The arteries mostly attacked are those of the heart and kidneys, and sometimes those of the mesentery, liver, spleen, stomach, intestines, muscle, etc.—more rarely those of brain or lungs. In these organs and tissues, secondary changes, such as infarction, necrosis and hæmorrhage, ensue from blocking of the arteries. In a case described by Beattie and Douglas, death resulted from rupture of an aneurysm in the kidney, and there was a deposit of fibrin in, and a leucocytic infiltration of, the adventitia of the affected arteries. The cause of the condition is unknown, though the general histological appearances, in the case described by Beattie and Douglas, suggested a bacterial infection (possibly secondary), and the clinical history supported this view. No organisms were demonstrated in the actual vascular lesions, but a pure growth of streptococci was obtained from the blood around the ruptured aneurysm. Most writers, however, are agreed that, though probably infective, the nature of the infection is non-bacterial. **Chronic cases** have been described in which the reparative changes probably prevented the formation of aneurysms. The vessels showed irregular nodular thickenings resembling those seen in thrombo-angiitis obliterans (Buerger's disease, pp. 482–3).

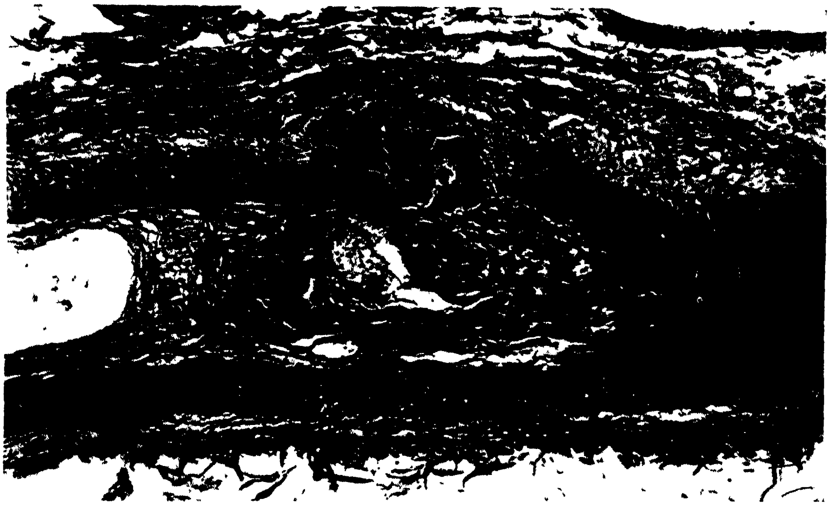

FIG. 273. *Acute Nodose Polyarteritis.* Longitudinal section of a small artery from mesentery, showing break in internal elastic lamina and muscular coat, and formation of minute aneurysm. Organising thrombus in lumen. Carnegie Dickson's case (*see* p. 478). (Unna's modified orcein-method for elastic tissue.) × 100.

2. PROLIFERATIVE ARTERITIS :—

(i) **SYPHILITIC DISEASE** (pp. 80 and 1008 *et seq.*). Syphilis affects the arteries in various ways—for example as a **panarteritis,** when all three coats of the vessels are attacked, though often in varying degree. The earliest histological change is a **periarteritis** with cellular infiltration of the adventitia around the small vessels, extending inwards and producing the condition of **endarteritis proliferans.** The essential lesion, in all cases, is the formation of young granulation-tissue, which, at a later period, undergoes transformation into well-formed fibrous tissue. According to most observers, the lesions of the aorta caused by acquired syphilis are found especially in the ascending part of the arch ; and, in early and more acute affections, the patches or plaques have a thick, raised, almost " fleshy " appearance, and are semi-translucent, pale, white, or slightly pinkish in colour. Later, when viewed from the intimal surface, they show a peculiar stellate scarring, with deep furrows and extensive endothelial proliferation. Calcification is not common. Microscopically, there is an abundant infiltration of lymphocyte-like and plasma-cells following the distribution of the vasa vasorum, destroying locally the elastic and muscular elements of the media, and causing extensive gaps in this coat. These gaps are ultimately filled by fibrous tissue, and a thickening of the intima takes place over them. *Treponema pallidum* is found in the more acute cases, often in considerable numbers, in these areas in the media. The vasa vasorum show endarteritis proliferans. Aneurysmal dilatation is common and its occurrence is explained by the prominent degree of mesarteritis (p. 493).

Syphilitic endarteritis, according to the late Professor Greenfield, is illustrated most typically by the proliferative or obliterative form of the disease

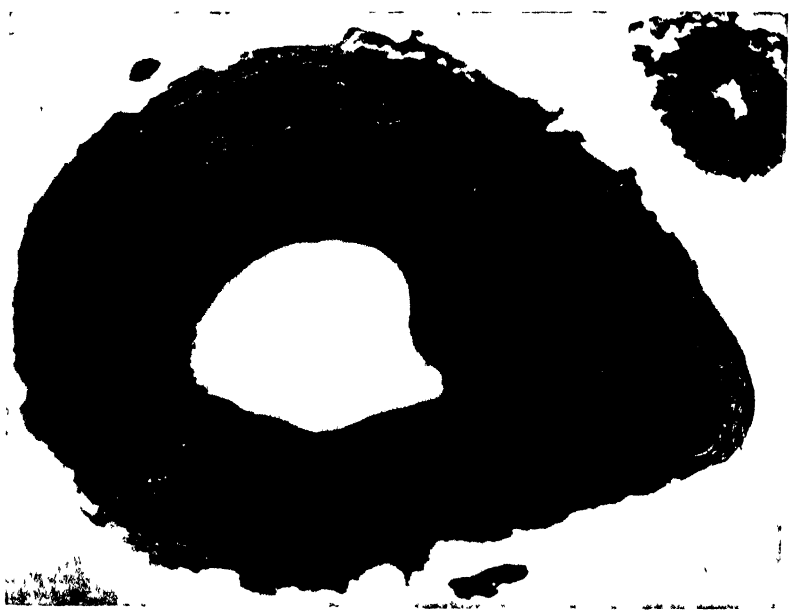

FIG. 274. Syphilitic artery, showing thickening of the inner coat, internal to internal elastic lamina (endarteritis proliferans), and also periarteritis. × 30.

seen especially in the arteries of the brain (Fig. 274, and *cf.* Figs 601 and 606–7, pp. 1003 and 1007). The change is usually widespread, but sometimes it may select one or, more frequently, a group or system of vessels in certain organs or tissues.

The inner coat becomes thickened by the formation of more or less regular concentric laminæ of fibrous tissue, which may greatly narrow, or even obliterate, the lumen. Between the connective-tissue laminæ, elongated cells are found—the relative proportion between these two sets of structural elements varying with the rapidity or the chronicity of the change. If growing rapidly and in the early stage, the newly-formed tissue is more cellular ; if developed slowly and of some standing, more fully-formed fibrous tissue is seen. In the process of formation of this new tissue, young, thin-walled capillaries are developed. These grow from the vasa vasorum, penetrate the internal elastic lamina, vascularise the new tissue, and so help to maintain its nutrition.

It is on account of this vascularisation that degenerative and necrotic changes, such as occur in the nodular form of atheroma, are absent in this variety of endarteritis. The newly-formed tissue of the intima consists of actively-developing granulation-tissue. According to many authors, the intimal proliferation is a compensatory reaction secondary to the medial change. We, however, regard the intimal change as the result of a chronic inflammation caused by the infective agent of syphilis acting directly on the inner coat of the vessel, *Treponema pallidum* being found in this coat, though it is also present, as already stated, in the degenerated areas of the media. The middle coat usually shows some cellular infiltration and necrosis, with absorption of muscle. Fibrous change is present when the condition is at all advanced. The internal elastic lamina is usually unaffected, but there may be new formation of elastic tissue (Fig. 275). The outer coat generally shows active proliferative changes, with accumulations of small lymphocyte-like cells, and the formation of granulation-tissue. This syphilitic periarteritis is seen especially around the small arterioles (Fig. 601, p. 1003) and vasa vasorum. The cellular infiltration may extend into the lower layers of the media, where the spirochæte is also found. Syphilitic disease is an important cause of atheroma, especially in the aorta (p. 484).

Effects. Syphilis, especially when it attacks some of the larger vessels, *e.g.*, the aorta, carotids, basilar and other cerebral arteries, cœliac axis, etc.—causes degenerative and fibrotic changes and loss of elasticity. Dilatation, often very irregular in type, occurs and leads to the formation of aneurysms (p. 493); but aneurysmal dilatation of the larger vessels may also be produced by syphilitic endarteritis causing obliteration of the vasa vasorum, the consequent loss of nutrition leading to degeneration and weakening of the wall of the large vessel.

The narrowing of the vessels may give rise to nutritional changes and over growth of fibrous tissue in the various structures to which they are distributed; or it may cause thrombosis in the vessel itself, just as do the changes in atheroma. This narrowing of, say, the coronary vessels, will lead to fibrous, fatty and other changes in the heart; and thrombosis in the small cerebral vessels will result in cerebral softening. The syphilitic affection may spread from the aorta to the cusps of the aortic valve, causing degenerative and proliferative changes, with consequent aortic incompetence. Distension or yielding of the aortic ring results in the separation of the cusps at their commissures.

(ii) **TUBERCULOUS DISEASE.** The arteries may become involved in the local spread of a tuberculous focus precisely in the same way as are other tissues—the tubercles being found mainly in the adventitia ; and, in cases of tuberculous meningitis (p. 992), these changes are specially well seen in the pial and perforating vessels (Fig. 598, p. 996). The weakening of the vessel-wall produced by the caseation may lead to aneurysmal dilatation. In the development of tuberculous lesions, obliteration of the vessels takes place in the nodules themselves. though there may be increased vascularity around them. Periarteritis and endarteritis obliterans in old-standing tuberculous affections are common.

(iii) **ENDARTERITIS OBLITERANS.** In this disease the main feature is a concentric thickening of the intima, without the occurrence of degenerative and necrotic changes in the proliferated tissue. The thickening may be so great that, in some instances, the lumen of the vessel is almost, or even completely, obliterated. The newly-formed tissue in the intima is often highly cellular and vascular, and is of the nature of granulation-tissue. Sometimes the new tissue shows concentric fibrous laminæ and a new formation of elastic tissue. Perivascular infiltration with the lymphoid type of cell may be present. The media may show little or no change. This is well illustrated in the proliferative and obliterative changes which take place in the vessels during the healing of a wound, and in chronic irritative or inflammatory diseases such as tuberculosis, leprosy and syphilis (Figs. 274 and 275). It is also seen in chronic renal disease, especially in that form in which advanced glomerular changes are present, and in chronic lung diseases in which fibrosis is a special feature, for example, in silicosis. A similar process occurs in the intima during the organisation of thrombi (Figs. 27 and 28, pp. 51 and 52).

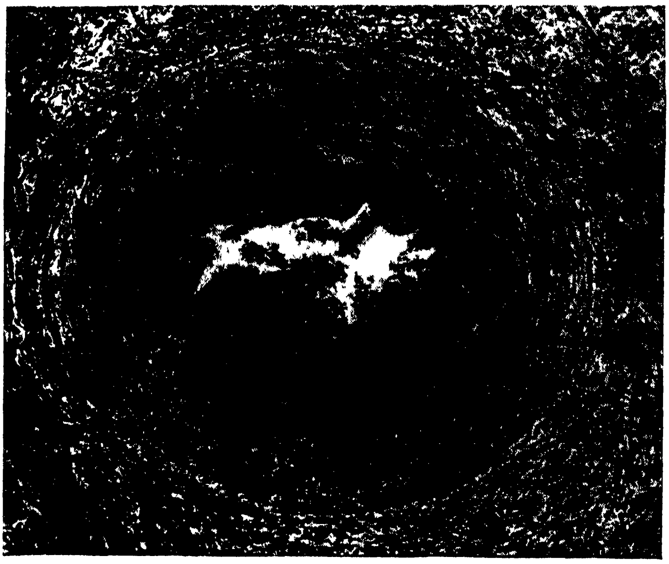

FIG. 275. *Endarteritis obliterans* in an artery from the tissue in the base of a chronic gastric ulcer. × 100.

(*a*) **Ayerza's disease.** A type of endarteritis obliterans, characterised by **extreme cyanosis** and by considerable hypertrophy of the right ventricle, has been described by Ayerza as occurring in the Argentine and other parts of South America. Narrowing of the pulmonary artery and its branches by fibrosis, with widespread intimal thickening, especially of the smaller pulmonary arteries, occurs. There is said by some writers to be no evidence that the changes are syphilitic in origin, but this is specifically denied by others, who even state that it is *usually* due to syphilis. **Polycythæmia** (p. 640) is a constant feature and red blood-counts as high as 11 to 13 millions per cmm. have been noted. This cyanotic type of erythrocytosis or secondary polycythæmia (the patients being called "black cardiacs") must be considered as a compensatory mechanism in respect to the pulmonary vascular sclerosis. Nephritis is said to be frequently associated with this disease.

(*b*) **Thrombo-angiitis obliterans** (*cf.* p. 244). This condition, which is often associated with severe cramp-like pains in the muscles of the calf of the leg and occasionally in the arms, was described by Buerger (1908, 1929). Most of the cases described have been in Hebrews—Russian and Polish Jews; but, in America, it has been found amongst immigrants of various races from Eastern Europe—not only Jewish, but, for example, Russians and Esthonians; and it attacks also Chinese and Japanese. It occurs practically only in males, and, in the majority of these, affects segments of the vessels, both arteries and veins of the lower limbs only. Gangrene and other trophic changes may supervene. Extensive thrombosis occurs and the thrombi are seen in various stages of organisation and canalisation. Buerger considers that the early stage is an acute inflammation of the walls of the vessels and their surroundings, and that a subsequent production of granulation-tissue gives rise to the formation of small nodules resembling tubercles, in which giant-cells are seen. In the later stages of the disease, fibrosis of the media and adventitia occurs, and this reaction may extend to and involve the surrounding tissues—muscles, nerves, etc. The cause is unknown, but the general pathology of the condition suggests an infective origin, possibly rickettsial in nature and believed by some to be allied to, or even identical with, that of typhus, of which certain writers believe it to be a late manifestation. Some workers have claimed that an excessive use of tobacco is an important factor in its causation.

(iv) **RHEUMATIC FEVER and ARTERIAL DISEASE.** There is general agreement that in rheumatic fever the tissues of the aorta, especially near its origin, may become infiltrated with lymphocytes and plasma-cells, and that, at special foci, the histocytic reaction is so pronounced that typical " Aschoff-bodies " (p. 471) are produced. The cellular exudate may extend to the media and cause a certain degree of necrosis of the muscle and elastic tissue ; but the damage to the wall of the vessel is generally so limited that liability to aneurysmal dilatation is not produced. American pathologists, and particularly von Glahn and Pappenheimer (1926), have described inflammatory lesions in the small arteries, especially of the viscera, in rheumatic disease. The walls of such arteries, in all their coats, are infiltrated with a cellular exudate which may be present also in the perivascular tissues. A minor degree of necrosis may occur in the media. Though thrombosis does not occur, these lesions in other respects resemble those described as occurring in **polyarteritis acuta nodosa** (p. 478), and some of the cases of this latter disease have been associated with attacks of what was thought to be acute rheumatic fever.

Though, as stated above, aneurysmal dilatation is not regarded as a result of acute rheumatism, Klotz has described the production of an acute saccular aneurysm in a boy of six years, during an attack of acute rheumatism with severe valvular disease, and, in this case, there was a well-marked mesarteritis. A streptococcus was grown from the blood and from the spleen. Similar changes, with necrosis, fibrin-formation and accumulation of leucocytes, have been recorded in pneumonia, in septic endocarditis, and in scarlet fever, and some authors regard rheumatism as an important factor in the production of many of the arterial thickenings seen in later life.

"**Raynaud's Disease**" or "**Syndrome**"[1] (pp. 187–8 and 244). In this condition, which, in its most characteristic form, is generally regarded as a disorder of the autonomic nervous system (pp. 1184 and 1193 *et seq.*), necrosis and gangrene, if they supervene, are due to contraction of the arteries resulting from a hyperexcitability of the vasomotor centre, resulting from lesions in the sympathetic ganglia (Figs. 764, and 765 to 768, pp. 1193 to 1197). Thrombosis of the vessels does not take place, though changes in the walls of the arteries have been described. Some writers regard the syndrome as due to hypersensitiveness of the arteriolar musculature to the action of cold, this increased sensitivity being, in certain of these patients, associated with the presence of the Donáth-Landsteiner cold-sensitised autohæmolysin (p. 661), and also with the occurrence of " spontaneous cold-hæmagglutination,"[2] *i.e.*, agglutination of the patient's erythrocytes when the temperature is sufficiently lowered—exposure to cold being thus an important factor in the production of all three of these phenomena.

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[1] Though " Raynaud's Syndrome " is now generally regarded as not primarily caused by " endarteritis " of any variety, it is convenient to insert a note upon it here, but with cross-references to pp. 187, 1184 and 1193 *et seq.*

[2] " Raynaud's Syndrome with Spontaneous Cold Hæmagglutination," by T. H. C. Benians and W. R. Feasby, *Lancet*, 1941, ii, 479.

3. CHRONIC ARTERIAL DISEASE: CHRONIC "ARTERITIS":—

(i) **CALCIFICATION,** secondary to degenerative changes, is comparatively common in arteries, but a form of sclerosis of the middle coat—**Mönckeberg's sclerosis**—presents certain special features. It is a senile degenerative change in which calcification in the media takes place. The distribution of the lime-salts is patchy, and the artery may be irregularly ringed by the deposit or it may be converted into a rigid tube. Proliferation of the inner coat is present in some cases, and the arteries may be dilated. Occasionally, ossification has been observed (Fig. 277). The arteries most commonly affected are the femoral, popliteal, radial and some branches of the iliacs. Thrombosis and gangrene may occur, but in such cases associated atheroma is usually present. The disease is not related to high blood-pressure. Hypervitaminosis-D (pp. 440–1) is associated with a rise in the calcium- and phosphorus-content of the blood, and the arteries, as a result of this, may show a calcareous infiltration of the middle coat.

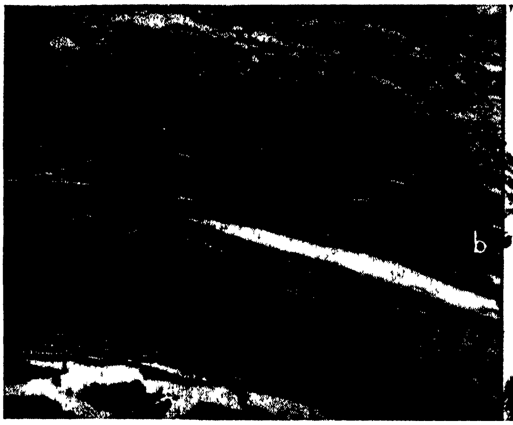

Fig. 276. *Mönckeberg's sclerosis,* showing vascularisation (*a*), and calcification (*b*), of all the coats of the artery. × 30.

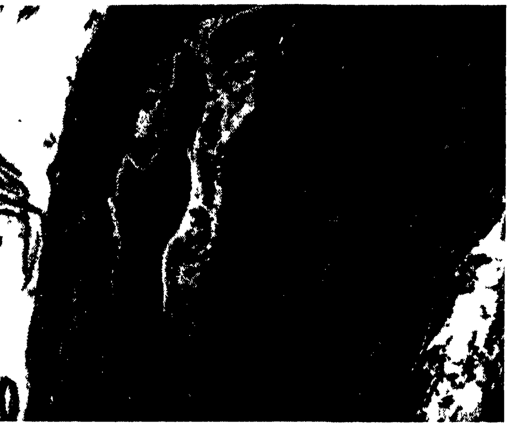

Fig. 277. *Mönckeberg's sclerosis,* showing the extreme degenerative changes and actual ossification (dark areas). × 30

(ii) **ATHEROMA.** The terms "atheroma" and "arteriosclerosis" have come to be used so loosely for general arterial degeneration and sclerosis that some authors have suggested that the two conditions should be grouped under one term, **atherosclerosis.** It is true that the two types of disease show many pathological features in common and that both may occur together in the same artery, but the changes differ in degree, in situation, in cause, and to some extent in kind. Atheroma is primarily a degenerative lesion, which, though occurring also in small arteries, is a disease especially of the large vessels, whereas arteriosclerosis is a diffuse fibrosis, generally associated with hypertrophic changes, seen particularly in the smaller arteries of the internal organs, associated with, and in many cases probably resulting from, high blood-pressure. We, therefore, propose to describe the conditions separately.

In **atheroma** or **endarteritis deformans** the essential lesion is a thickening of the intima, with varying degrees of degenerative changes in its deeper part, *i.e.*, the part most distant from the lumen of the vessel. The thickening is, commonly, limited in area, producing irregular patches or flattened nodules :

but it may, in other instances, be more diffuse and widespread, giving rise to general thickening and rigidity of the vessels.

(*a*) In the **nodular variety,** distinct elevated patches, with—to the naked eye, at all events—well-defined edges, are seen. At first, these nodular areas are a dull white or pale yellowish colour, on account of the fatty degeneration which occurs in the deeper part of the patches. As they become older, they tend to increase in size, adjacent patches coalesce, the fatty degeneration becomes more marked, and lime-salts are deposited in the degenerated areas. Thus are produced large, irregular, raised, pale-brownish, calcareous plaques and nodules in the inner wall of the vessel (Fig. 280). The continuity of the endothelium covering the patches is at first preserved ; but, later, this also undergoes degenerative changes and may become lost, and, as a result, thrombosis is liable to occur on the roughened patches. The calcified plates may crack across, and thus the blood in the vessel may burrow its way between the inner and middle coats, or between layers of the middle coat, and produce the condition of **dissecting aneurysm** (p. 496). The degenerated focus may soften and form a cavity containing fatty debris and crystals of the fatty acids, from the cheesy or gruel-like character of which the condition receives its name.[1] The tissue superficial to the cavity may eventually give way and thus form an atheromatous ulcer, in the walls of which calcification is present and on which thrombi may form. These degenerative changes may thus be a possible source of emboli, in the form of broken-off fragments of calcified plates, necrotic debris, or thrombotic vegetations.

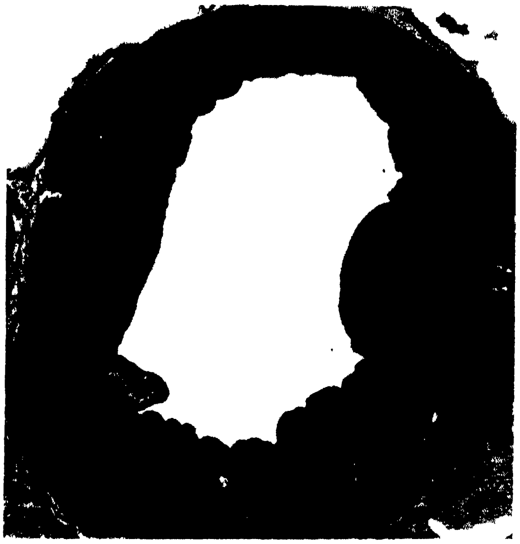

FIG. 278. *Radial artery*, showing an early patch of thickening of the intima (on the right). The elastic lamina is stained dark. × 28.

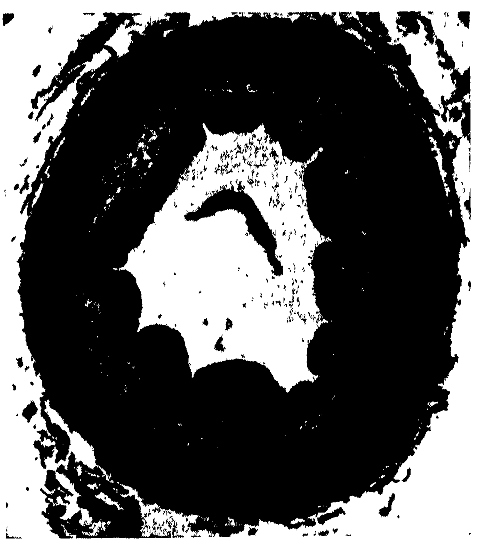

FIG. 279. *A medium-sized artery* showing early and irregular areas of thickening of the inner coat. × 25.

On microscopical examination (Plate IX, Fig. 4, p. 200), the change is seen to consist of a laminated thickening of the inner coat, due to proliferation of the subendothelial connective tissue, and perhaps also, as some writers believe, of the endothelium itself. In the early stages, many round, ovoid, or irregular cells are found between the connective-tissue strands. The thickening may be considerable in amount, and, in the layers farthest from the lumen, degenerated tissue containing neutral fat, lipoids, cholesterol, fatty acids and lime-salts are found. The elastic tissue in the larger arteries may become fragmented, but an increase of this tissue may arise by a splitting of existing fibres or by an actual proliferation and formation of new elements produced either by and in connective-tissue cells, or formed, according to some authors, by a gelation of a passive colloidal sol which has been secreted by the cells and fills the spaces between them. The gelation is said to be produced by some unknown factor, presumably an enzyme. In the smaller arteries, the internal elastic lamina becomes flattened out and fragmented, and, at places, it may entirely disappear. The muscular part of the middle coat may remain unaltered, but degeneration and atrophy of the muscle-fibres, with an overgrowth of fibrous tissue, especially opposite the site of greatest thickening in

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[1] The term ἀθήρωμα, *athērōma* (from ἀθήρη or ἀθάρη, *ăthērē* or *ăthārē*, or sometimes *ăthărē*, groats or meal, or porridge made from these) was used by Galen to denote "a tumour full of gruel-like matter" (L. and S.), *e.g.*, an "atheromatous cyst."

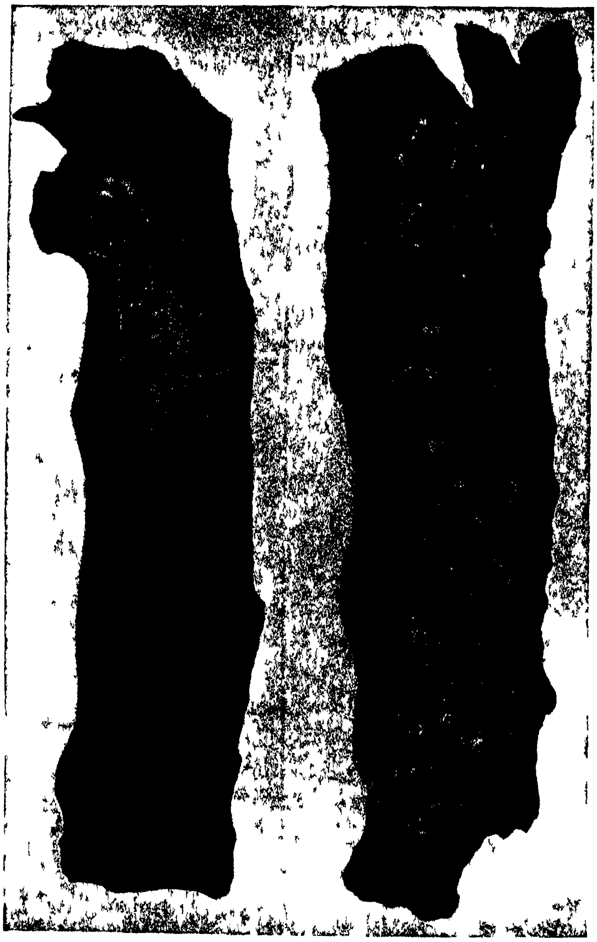

FIG. 280. *Atheroma of aorta.* In the left hand specimen the change is seen especially round the orifices of the arterial branches, in the other it is more advanced and widely spread

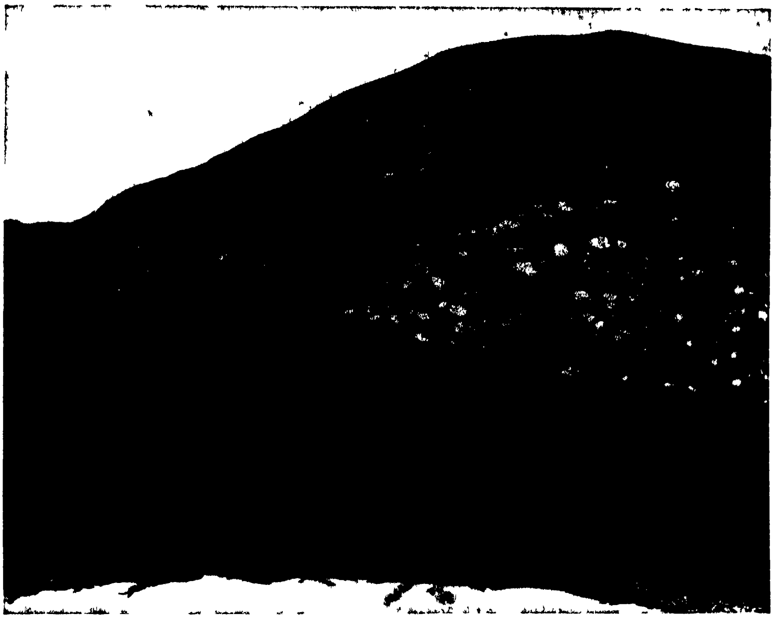

Fig. 281. *Atheroma of aorta*, showing (*a*) thickened intima with degeneration at deeper part, (*b*) media with no evidence of degeneration × 30.

the inner coat, are of frequent occurrence. There may be a deposit of lime-salts in the degenerated parts of the muscular coat ; or, in some cases, mucinoid degeneration occurs ; and the possibility of a new formation, not only of strands of elastic tissue, but of a definite elastic lamina, must be recognised. The outer coat may be unaltered, or a certain amount of fibrous hyperplasia be present in it.

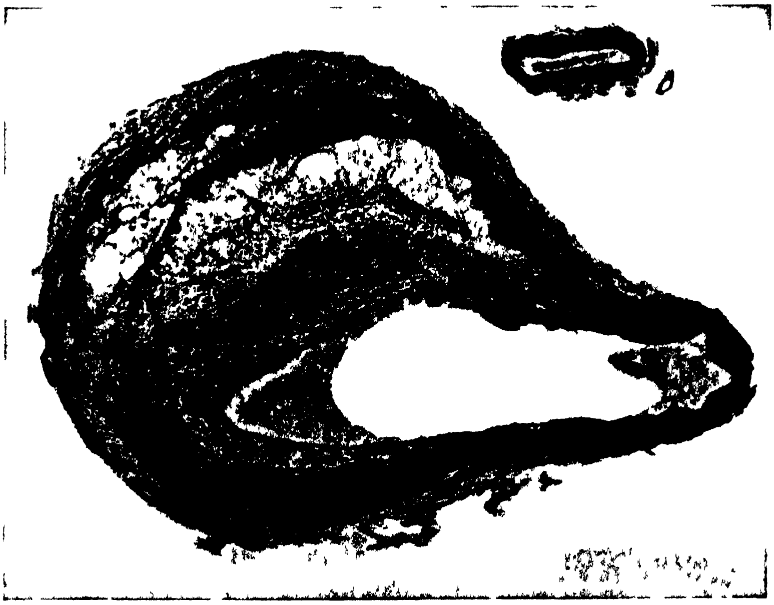

Fig. 282. *Atheroma* in a cerebral artery, showing the thickening and degeneration of the intima, the fragmentation of the internal elastic lamina, and the degenerative changes in a portion of the media. × 40.

(*b*) In the **diffuse form of atheroma,** the arteries are usually dilated, and, on section, in spite of the thickening of the inner coat, remain abnormally patent, though, in some cases, this thickening may be so great as to cause complete obliteration of the lumen. The vessels often become tortuous—this tortuosity being due to their loss of elasticity and consequent elongation.

On **microscopical examination,** the thickening of the inner coat is usually more or less uniform, and is made up of regular concentric layers of fibrous tissue. Fatty and other degenerative changes are found, and the deposit of lime-salts may convert the artery into a rigid tube. The muscle-fibres become atrophied and may eventually be replaced by fibrous tissue. The internal elastic lamina may lose its wavy character, and frequently is swollen and fragmented. The outer coat sometimes shows fibrous overgrowth.

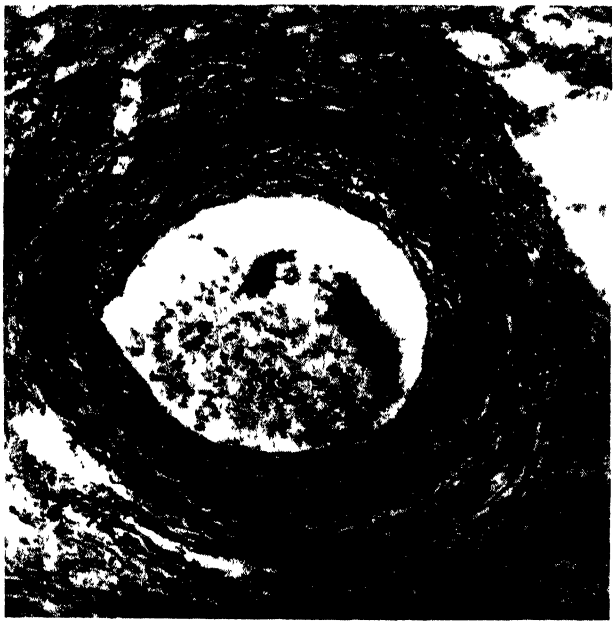

FIG. 283. *Diffuse arteriosclerosis* in a renal vessel, stained by eosin and Verhœff's elastic stain. × 110.

Sites of Occurrence. The nodular form is seen especially in the aorta and large vessels. In the aorta, the condition is most marked in, and may be confined to, the arch, in which the thickening and the degenerative changes supervene immediately above the valve-cusps and round the origins of the coronary arteries and the great vessels of the neck. When it occurs in the thoracic or abdominal aorta, the same advanced change is frequently seen round the origins of the intercostal, lumbar, and other arteries (Fig. 280), and also particularly at the bifurcation of the abdominal aorta into the common iliacs. The coronary arteries of the heart and the arteries of the brain (Fig. 619, p. 1029) may show this degenerative change in a more or less pronounced degree ; and the pulmonary arteries may also be affected, and in mitral stenosis even the smallest visible branches of these arteries may show the change. In the diffuse form, the medium-sized vessels, such as those of the kidneys, brain, or ovaries, are most commonly affected. The thickening of the inner coat may be so extreme as to cause complete, or almost complete, obliteration of the lumen of the vessel.

(iii) **ARTERIOSCLEROSIS.** In this disease, the arteries are hardened, often dilated, lengthened and tortuous, but the essential change is an increase of fibrous tissue in their walls. Arteriosclerosis may be widespread and the degenerative changes characteristic of atheroma entirely absent. Frequently, a concentric fibrous thickening of the tissue lying immediately under, *i.e.*, external to, the endothelium, is seen in the smaller arteries, with a consequent narrowing of their lumen. In this thickened zone, in the larger of the medium-sized arteries, hypertrophy of the longitudinal muscle-bundles which lie internal to the internal elastic lamina is generally observed, the lamina itself is thickened and may be double or multiple, and an actual increase of elastic tissue appears to take place. The media is thickened, resulting sometimes from a true hypertrophy of the muscle, but more commonly from an increase in fibrous tissue. Possibly the primary change is hypertrophy of the muscle, followed by atrophy and fibrous replacement. In young subjects, cases have been described in which pure muscular hypertrophy was the cause of the medial thickening. The elastic tissue in the media is also increased in the early stages, but, when fibrosis is becoming a prominent feature, these elastic fibres undergo granular degeneration and eventually disappear. The adventitia usually shows an increased fibrosis. These changes, though general in the smaller vessels of the arterial system and particularly in the arteries of the internal organs, are often most prominent in the arteries of the kidneys, where the vessels may be seen, on naked-eye examination of the cut surface, as whitish rings with an open lumen.

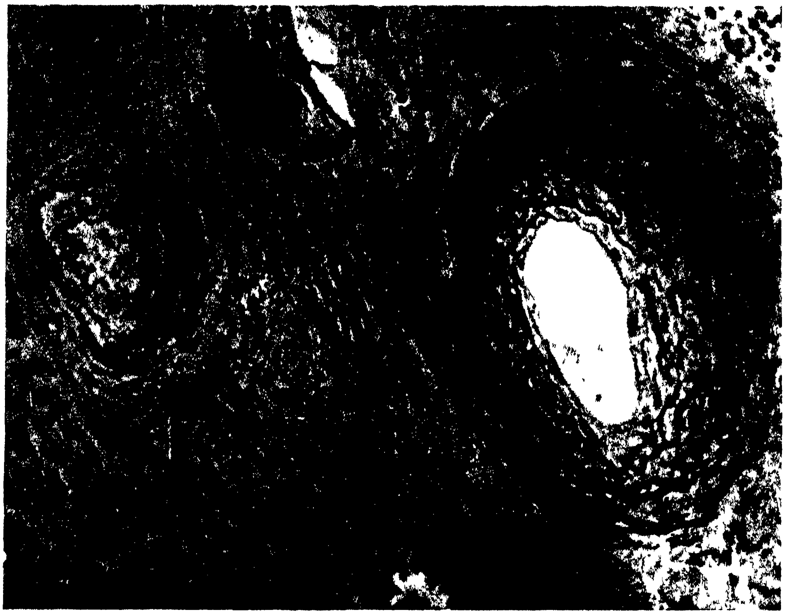

FIG. 284. *Thickened arteries* in the kidney, showing increase in elastic tissue. × 200.

Pathogenesis of Arterial Disease. Though various factors are known to be causal of arterial lesions, yet the manner in which they act is still an only partially solved problem. Patches of early atheroma are frequently found immediately above the valve in the aortas of young children, and even of infants, and it is so common in old age that a certain degree of it may be considered almost "physiological." The sites at which atheroma occurs point specially to friction or strain as being an important causal factor. Thus, in the aorta, the condition is always most pronounced in that part of the arch which is most exposed to the impact of the blood during the systole of the heart, and at the orifices of branches, where the friction and strain are also great. Again, in cases of congenital narrowing (coarctation) of the aorta (pp. 447–8) there may be very evident atheroma on the proximal side of the stricture, whilst the vessel-wall on the distal side may be unaffected. In the pulmonary artery, the condition is observed especially where there is increased pressure in the vessels, as, for example, in cases of chronic venous congestion arising from obstruction at the mitral orifice, combined with hypertrophy of the walls of the right ventricle.

According to Thoma and various other observers, the changes are due to the adaptation of the vessel to the diminished velocity of the blood-stream produced by the inability of the middle coat to.contract, the amount of blood flowing through the vessel being regulated mainly by the calibre of the artery. They believe that there is a primary degenerative change in the muscular coat, which leads to a loss of its power of contraction. The vessel thus becomes dilated at these degenerated areas, and, in order to make up for this dilatation and slowing of the blood-stream, compensatory thickening of the inner coat takes place. If the rate of flow were reduced to one-half, the sectional area of the vessel, they believe, would be diminished to one-half, and the channel would be about half the normal. If this diminution cannot be brought about by muscular contraction, it will, they maintain, occur by a gradual fibrous thickening of the inner coat. We cannot, however, agree with this hypothesis which of necessity postulates some primary damage to the middle coat. Though this primary muscle-degeneration may sometimes occur, the proliferative and degenerative changes which have been described may be present in an artery, the media of which is apparently healthy ; and, moreover, in many cases, the change in the media appears to be the result, and not the cause, of the alteration in the intima.

In rabbits fed for several months on a diet containing cholesterol, McKee (1914) and other workers found degeneration and calcification in the media of the aorta, but not in the smaller arteries, and Klotz showed experimentally, by inoculating animals either with typhoid bacilli or with pyogenic streptococci, that thickening of the intima may be produced without any obvious change in the media, and, apparently, by the direct action of bacteria or their products on the intima itself. In these experiments he noted also the occurrence of fatty degeneration of the endothelium, splitting and fragmentation of the internal elastic lamina, and proliferation of connective tissue. He claimed, therefore, that atheroma could be produced by the direct action of bacteria or their products on the vessel-wall. According to Klotz, Rickett and others, these extensive degenerative changes in the muscular coat are not necessarily followed later by proliferative changes in the intima.

The more commonly accepted view is that the thickening of the intima is the direct result of excessive pressure or strain, or of the action of toxins upon the walls of the vessels, or of a combination of these ; and that it is more liable to occur in vessels in which the elasticity of the muscular coat is impaired by malnutrition or other cause. Increase of pressure in the vessels may bring about a loss of elasticity, and this probably explains why, in cases of muscular overwork, or in an individual in whom the heart is hypertrophied, arterial degeneration commonly occurs. Suggestive work by Winternitz (p. 477) and his co-workers (1938) seems to indicate that the atheromatous change may be determined by lesions in the vasa vasorum. They maintain that vasa vasorum take origin in the adventitia and also from main arteries, especially at the openings of branches from the parent vessel, and that the vascular network found in the arterial wall is due to anastomosis of intimal and medial vessels with those of the adventitia as well as of branches given off from the lumen of the parent vessel (the intimal feeder). Hæmorrhage into the subendothelial tissue from these vasa is frequent, and is found principally at the points where the branches leave the parent artery. It is at these sites that atheroma generally occurs, and it is not unreasonable to assume that such hæmorrhages may be the starting-point of the proliferative reaction, and that the vasa are the channels by which bacteria or toxins are carried to these hæmorrhagic and damaged areas. In atheromatous patches, these authors have, by injection-methods, demonstrated a rich network of vessels derived from the vasa vasorum, with finer ramifications lying just beneath the endothelium (*cf.* p. 477).

The almost constant association of chronic nephritis with arterial disease suggests a relationship between the two conditions ; and the non-elimination by damaged kidneys of effete and toxic products, and the consequent absorption of these substances into the tissues, may play some part in its production.

It is known that, in lead-poisoning and gout, vascular changes occur, and it seems highly probable that the absorption of products of abnormal metabolism, bacterial products and substances of a similar nature can and do cause proliferative and degenerative changes in vessels. Hyaline degeneration of the arteries of the spleen and kidney in typhoid and other fevers, and the changes produced experimentally in rabbits by the injection of cholesterol or bacteria, also support this view.

Increased blood-pressure, so frequently associated with chronic nephritis and sometimes primarily due to disease of the kidneys, is regarded as a causal factor in such reactive changes as occur in arteriosclerosis. In the majority of cases, however, it is difficult to assign a definite cause for the increased blood-pressure. It is true that, in cases of primary arteriosclerosis, chronic changes may be present in the kidneys, but these are frequently secondary to the arteriosclerosis and consequent impaired blood-supply. In other instances, the arteriosclerosis is present, *pari passu*, with comparatively healthy kidneys. Other causes, therefore, of this increased blood-pressure must be sought.

Goldblatt and his co-workers [1] in America have, from 1934 onwards, focussed attention on the primary importance of the kidneys in the pathogenesis of arterial hypertension, and, by graduated clamping of the renal arteries in dogs, they have been able to produce a definite hypertension (p. 869). By varying the degree of narrowing of the lumen of the artery hypertension of the benign type (hyperpiesis or hyperpiesia), with little or no functional disturbance of the kidney : or of the malignant type, with definite and real damage of the kidney, could be produced at will. Goldblatt suggested two possible mechanisms for this phenomenon, both originating in the ischæmic kidney ; (1) a reflex nervous stimulation of the general vasomotor apparatus, and (2) the action of some substance produced in the ischæmic kidney and possibly accumulating in the blood as a result of non-elimination. This hypothetical " pressor " substance has been called " renin," and is believed by some investigators to require activation by a substance or substances normally present in the blood—with the formation of a derivative termed " angiotonin," which is said to act directly upon the smooth muscle in the walls of the blood-vessels. Further work on this important subject is required before any definite pronouncement can be made upon it. There is some evidence from these experiments that the removal of the adrenals abolishes or prevents hypertension. A possibly analogous rise of blood-pressure has been observed to occur in certain cases of infarction of the kidney, and has been attributed to the ischæmic changes thus more suddenly produced in the renal tissues by the blocking of some portion of one of the renal arteries by embolism or thrombosis—the hypertension then gradually subsiding as the kidney recovers from the effects of the infarction.

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[1] H. Goldblatt, J. R. Lynch, R. F. Hanzal and W. W. Summerville, *Jour. Exper. Med.*, 1934, **59**, 347 ; H. Goldblatt, *Amer. Jour. Clin. Path.*, 1940, **10**, 40 : M. Prinzmetal, H. A. Lewis and S. D. Leo, *Jour. Exper. Med.*, 1940, **72**, 763.

FIG. 285. *Ovary* : arteries showing marked thickening of inner coat. × 90.

Whatever the cause of the high blood-pressure and vascular hypertonus, the sequence of events leads ultimately to fibrosis and loss of elasticity in the vessels, and, it may be, to fibrosis in the organs supplied by the vessels, and especially in the kidneys.

Degenerative changes in the arteries without evidence of high blood-pressure and with no hypertrophic changes are frequently seen in old people and have sometimes been rather loosely described under the term "arteriosclerosis." They are in reality cases of fibrosis secondary to degeneration of the muscular and elastic tissue.

Effects of Sclerotic Changes. The vessels may be considerably narrowed, and, if this happens in the medium-sized and smaller arteries such as those conveying blood to the heart, brain, kidney, or extremities, there may be pronounced nutritional changes in the areas supplied. Thus, in the heart, there may be some atrophy of the muscle-fibres and replacement of these by fibrous or fatty tissue; or, if a branch of one of the coronary arteries becomes thrombosed—a not uncommon result of the degeneration and narrowing—infarction and necrosis occur. In the brain, softening is the usual result: and, in the kidneys, fibrosis and other degenerative changes.

The narrowing of the peripheral vessels constitutes an impediment to the blood-flow, and hence to the action of the heart; and this leads to hypertrophy of its wall, especially of the left ventricle. The rigidity and the loss of contractility and of elasticity of the artery-walls produced by the proliferative and degenerative changes are important factors in the causation of aneurysms.

ANEURYSM

An aneurysm may be defined as a more or less circumscribed dilatation of a vessel or of the heart-wall, its contents being blood: or blood-clot of varying age, perhaps laminated: or an admixture of blood and clot. The term, however, is also somewhat loosely used for localised collections of blood, either between or in the coats of the vessel-wall, or even for collections which are surrounded by a more or less well-defined envelope, though they be altogether external to an artery. We propose, here, to confine our description to "aneurysms proper," *i.e.*, dilatations of vessels, and particularly of arteries; whilst aneurysms of the heart are described on p. 467, and dilatations of veins are referred to later (p. 499).

Ætiology. Aneurysms are due to local weakening of the vessel-wall, and their production is aided by any increased pressure within the vessel. The condition is of most frequent occurrence in persons about the age of forty or forty-five, and in those whose vessels show degenerative changes in the muscle and elastic tissue. The commonest primary cause is syphilis, the lesion in the aorta being predominantly a mesaortitis (pp. 480–1). Aneurysms, however, may occur in non-syphilitic individuals. In such cases, the dilatation generally begins at areas of local weakness in the media either congenital in origin or due to spread from disease of the intima in atheroma. In the aorta, the common site of damage is under a calcified atheromatous plaque. The production of sacculation at the weakened area is aided by increased blood-pressure, and, for this reason, aneurysms are found most frequently in those who are subjected to severe muscular strain and the lesion is, in general, therefore, much commoner in males than in females. Aneurysms of the cerebral arteries (p. 1042 *et seq.*), which sometimes occur in young people, are, however, commoner in females than in males. They are thought to be due to congenital deficiency in the middle coat (pp. 495 and 1043 *et seq.*). The occurrence of aneurysms in chronic renal disease is due mainly to the degenerative changes in the wall of the vessel brought about by the chronic toxæmia, but there seems little doubt that the persistent high blood-pressure is an important contributory cause. The degenerative changes and the loss of contractility and elasticity in the media diminish the resistance to the distensile force transmitted by the blood; and probably, in the majority, if not in all, of the cases, this degeneration is essential to the production of the dilatation. Destructive changes in the walls of the arteries may also be produced by direct injury: by the spread of ulceration from outside, *e.g.*, aneurysm of the splenic artery resulting from the involvement of that vessel in ulceration of the stomach, or aneurysm of a branch of the pulmonary artery due to destructive changes in a phthisical cavity : or by sepsis involving the artery from within, as occurs in septic embolism, or in the local spread of ulcerative endocarditis into the aorta. These are known as infective or mycotic aneurysms.

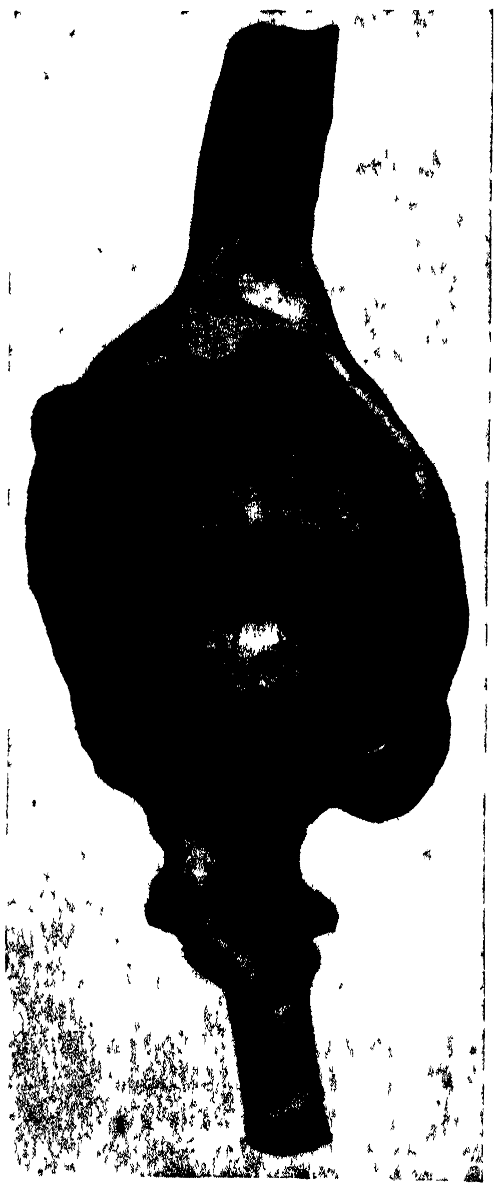
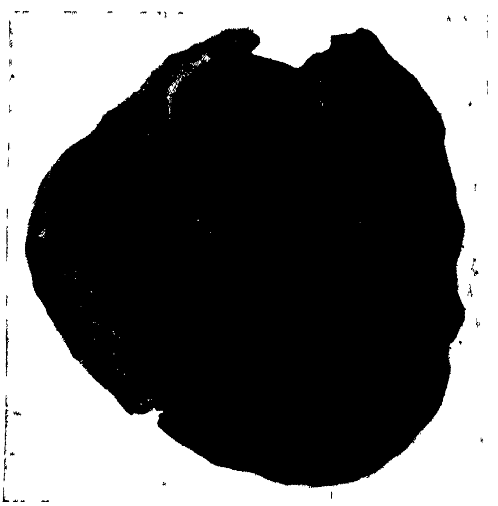


FIG. 286. *Aneurysm of abdominal aorta filled with thrombus.*

Sites of Aneurysms. The artery most commmonly affected is the aorta, and, in particular, its thoracic portion. The aneurysm starts, as a rule, in the region of the sinuses of Valsalva (sinuses of the aorta), and, eventually, may involve especially the ascending part of the arch. Sometimes, the aneurysms are multiple, and an aneurysm of the thoracic aorta may be associated with one or more originating from the abdominal aorta. Aneurysms of the medium-sized and smaller arteries such as the coronary, splenic, mesenteric, renal, or popliteal, are generally associated with degenerative changes in the wall (atheroma or arteriosclerosis). Aneurysm of the popliteal artery was said to be common in those who did much riding, such as post-boys and cavalry-soldiers. Though degeneration in the wall was probably the primary factor, this was aided by the bending of the vessel on account of the flexed position of the limb and by repeated slight trauma. Aneurysm in this position is now rare.

Aneurysms of the main cerebral arteries, comprising those of the circle of Willis (circulus arteriosus) and its branches, are common, though many of them are small (Fig. 634, p. 1042). They tend to arise especially at bifurcations, the junction of the anterior communicating and anterior cerebral arteries being a common site. They are due in part to congenital deficiency of muscle-coat at the bifurcation and in part because small vascular twigs take origin at this situation (Fig. 635, p. 1043). Several such intra-cranial aneurysms may be present in one individual at different vascular bifurcations (Fig. 634). Rupture is a common termination, often preceded by small and sometimes recurring leaks. Blood is found in the cerebrospinal fluid and is a useful diagnostic feature. The blood is effused at the base of the brain, often obscuring its point of origin and giving an appearance not unlike hæmorrhage from fracture of the base of the skull. Sometimes they rupture into the brain-substance, causing laceration (p. 1045 *et passim*).



showing the method of formation in laminæ.

The presence of minute or "miliary" aneurysms on certain of the small arteries in the substance of the brain has been thought by many writers to be one of the chief causes of cerebral hæmorrhage. They are, however, probably not of such frequent occurrence as was previously believed, and our readers will find the problem discussed on pp. 1038 and 1042–3. Small aneurysms on the retinal arteries may by their rupture lead to hæmorrhage in that situation, and are to be distinguished from angiomatosis of the retina (von Hippel's disease) not infrequently associated with Lindau's syndrome (p. 1131).

Aneurysms resulting from infective emboli from the valves of the heart are found most commonly on the middle and anterior cerebral arteries, though they may develop also on peripheral vessels.

Varieties and Structure. True aneurysms may be divided into two main varieties :—

1. Those in which there is primarily a general, and more or less uniform, dilatation of all the coats of a vessel—the **fusiform** aneurysm. As the dilatation increases, there may be thickening of the inner and outer coats, with atrophy of the media. This atrophy is usually only partial, but, at places, there may, especially in long-standing cases, be complete disappearance of the muscular tissue. More rarely, the inner coat also undergoes atrophy.

2. Those which are really pouches from the vessel—a local unilateral dilatation taking place at a weakened part of the vessel-wall. These **saccular** aneurysms usually communicate with the vessel by a relatively narrow opening. The wall of the aneurysmal sac, like that of the fusiform aneurysm, may show evidence of the persistence of the three coats of the vessel, with, however,

the media usually atrophied and the intima thickened and atheromatous. In other cases, it may be impossible to trace the constituent coats.

Thrombosis is common in the saccular class of aneurysm, and the thrombus tends to be deposited in successive layers (Figs. 286 and 287), more or less completely filling up the sac. If the aneurysmal sac is small, complete healing is sometimes brought about by this process of thrombosis and organisation.

In "**dissecting aneurysms**" resulting from degenerative changes in, or from mechanical injuries to, the intima, the blood in the artery makes its way between the inner and middle coats or between layers of the middle coat, and burrows, it may be, for considerable distances. By rupture of the wall of the vessel, the blood may eventually make its way either externally, or back into the lumen. These so-called "aneurysms" are found most commonly between layers of the middle coat, and may cause atrophy of the muscular tissue. They may arise through the cracking across of an atheromatous patch; but they occur also as the result of ulceration spreading from the aortic valves and involving the first part of the aorta.

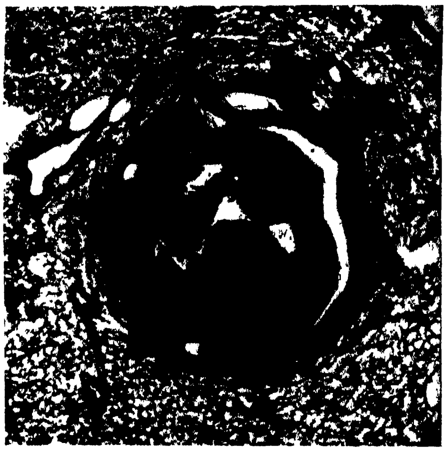


FIG. 288. *Small aneurysm* in left lung. Shows central irregular cavity with organised thrombus around. The thrombus is retracted from the wall at one side. The aneurysm had ruptured into a bronchus. Unstained. × 5.

Tyson[1] (1931) states that the usual mechanism is a rupture of one or more vasa vasorum into a degenerated tunica media, and that the blood in this hæmatoma is then forced by the pressure in the aorta to burrow along and around that vessel. The tear in the tunica intima, if present at all, is thus, in his opinion, the result and not the cause of the condition.

Shennan[2] (1934), of Aberdeen, has described a series of examples of "dissecting aneurysm" of the aorta, in which the presence of any gross lesions of the intima was exceptional, his conclusion being that a causal factor common to all of his cases was degeneration, diffuse or localised, of the **media**—the diffuse alterations being fatty and atrophic changes in the **muscle,** often with complete disappearance of the fibres in small areas of the wall: hyaline and other forms of degeneration of the **connective tissue,** with occasional deposit of calcareous salts: swelling, varicosity and fragmentation of the **elastic laminæ**: and the development of local "faults" in the media, varying from the earlier degenerative and necrotic changes up to old scar-formation—all such cases do *not* invariably end fatally—the media usually giving way before the intima. As a result of pressure, the intima is bulged into this degenerated part of the media and may rupture. The plane in which the blood travels is determined partly by the site of the degeneration in the middle coat.

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[1] "Dissecting Aneurysms," by M. D. Tyson, Yale University Medical School, *Amer. Jour. Path.*, 1931, 7, 581.

[2] "Dissecting Aneurysms," by T. Shennan, Medical Research Council Special Report Series, No. 193, London, 1934.

The so-called "**false aneurysm**" is really a hæmatoma. As a result of a perforating wound or of rupture, accidental or spontaneous, of a vessel, the blood escapes into the surrounding tissues, where it becomes encapsulated by condensation of these tissues, or by their inflammatory or irritative proliferation.

Sometimes a wound perforates both an artery and a vein, a direct connection may be established, and the vein becomes distended by the blood which passes in from the artery. Such a condition is known as an **aneurysmal varix.** Again, the connection between the two may not be direct, but may be by a channel through an adventitious sac formed by a condensation of the intervening tissues, and to such the name **varicose aneurysm** is applied. A varicose aneurysm may also be produced by a saccular aneurysm pressing upon, and eventually opening into, a vein.

The terms "Cirsoid Aneurysm," "Racemose Aneurysm" and "Anastomotic Aneurysm" are applied to conditions where there is a mass composed of dilated and thickened vessels—especially in the subcutaneous tissues of the scalp. These are usually congenital malformations; there is no true aneurysmal dilatation, and the term "aneurysm" in connection with them is wholly misapplied.

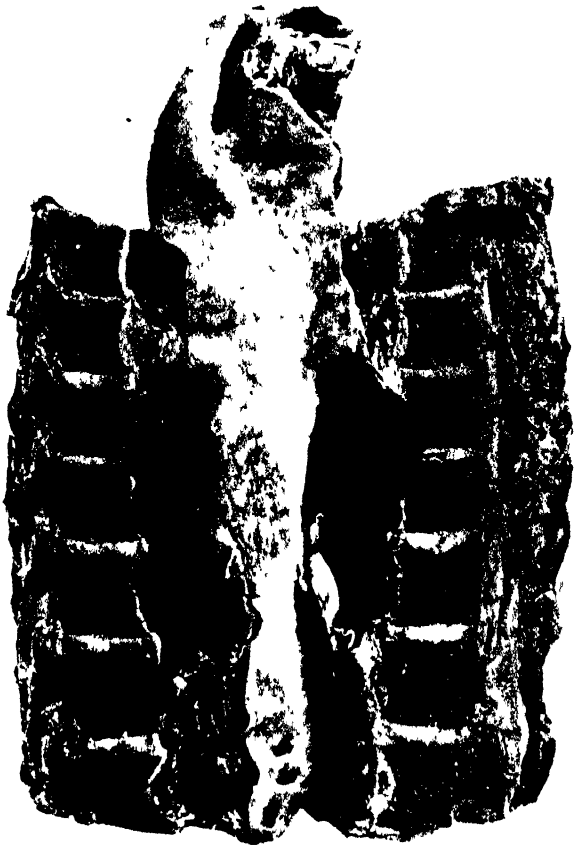

Fig. 289. Section through an aneurysm of the descending aorta, eroding the vertebræ, the bodies of which are more affected than the intervertebral disks which are seen projecting into the cavity of the aneurysm. This has been opened into from behind by mesial section through the spine, the two halves of which have been separated from each other.

Conditions associated with, and Terminations of, Aneurysms. The general tendency of aneurysms is to enlarge progressively—the surrounding tissues being pushed aside or absorbed as a result of the pressure. The enlargement is not always in the direction of what appears to be the line of least resistance. Thus, an aneurysm of the thoracic or abdominal aorta may enlarge posteriorly and cause erosion of the vertebral bodies, even coming to press on the spinal cord. In this erosion, the intervertebral disks, because of their elasticity, do not suffer to such a degree as the vertebræ themselves, and may be seen projecting beyond the surface of the eroded bones (Fig. 289, above). Enlargement may, however, take place in any direction, and thus pressure upon important structures and interference with their function may arise, or they may even be completely destroyed. An aneurysm of the thoracic aorta may press on and erode the sternum; may cause compression of the trachea or bronchi, and thus produce collapse of the lungs; may compress and open into some of the larger veins; or may cause laryngeal paralysis by pressure on the left recurrent laryngeal nerve. Compression of the optic chiasma, tracts and nerves may be caused by intracranial aneurysms, especially by those of the intracavernous or subclinoid portion of the internal carotid artery or of the circulus arteriosus (circle of Willis), and give rise to certain nerve-palsies, *e.g.*, oculo-motor lesions (p. 1045).

Hypertrophy of the left ventricle is frequently described as occurring in cases of aneurysmal dilatation; but, in our experience, it is *not* usual, unless there is some associated narrowing or dilatation of the aortic orifice, or the presence of some independent cause of hypertrophy, *e.g.*, chronic nephritis.

Spontaneous cure by thrombosis and organisation is rare. Rupture may occur in any situation or into any adjoining cavity, organ, or tissue. Aneurysms of the thoracic aorta may burst into the pericardial or pleural sacs, into the trachea or bronchi, into the œsophagus, the vena cava, the mediastinum, or, much more rarely, externally, after the skin has become stretched and eroded. Intracranial (including intracerebral) aneurysms may cause subarachnoid or cerebral hæmorrhage, and give rise to localised nerve-palsies, or to complete or partial hemiplegia.

II. DISEASES OF CAPILLARIES AND SMALL VENULES

The capillaries and venules, as a result of long-standing strain, may undergo hypertrophy and thickening, combined with varying degrees of dilatation. In cases of long-standing venous obstruction, this condition is well seen in the capillaries of the lung, and in those of the glomeruli in the kidney. The hypertrophy or thickening is shown, microscopically, by the presence of a more or less well-developed layer of fibrous tissue external to the endothelium, and it seems probable that this is derived from a pre-existing and very delicate peri-endothelial (perithelial) layer of fibrous tissue.

DEGENERATIVE CHANGES such as cloudy swelling and fatty degeneration are common in the endothelial cells of the venules and capillaries in conditions which give rise to these alterations in other organs and tissues. Hyaline degeneration in the glomerular capillaries in the kidney, and in the vessels in the spleen and other organs, is often present in scarlet fever, diphtheria, and certain other toxic diseases. Amyloid degeneration when present is demonstrable in the supporting connective tissue of the capillaries. Pigment, taken up by the endothelial cells, which are actively phagocytic, is seen in areas where there have been hæmorrhages or in diseases in which blood-destruction is a prominent feature, *e.g.*, malaria. A certain amount of pigmentation of the endothelial cells of the cerebral capillaries appears to be a normal finding, and is increased or exaggerated in many pathological conditions.

III. DISEASES OF VEINS

DILATATION AND VARICOSITY. The veins possess a great capacity for dilatation, and, therefore, any mechanical obstruction to the circulation or any weakness of the walls of the veins themselves may give rise to great enlargement. The obstruction in one vein leads to obstruction and distension of its tributaries. Thrombosis of the deep veins of a limb is often followed by varicosity of the superficial veins. Accompanying the dilatation, if it is not merely transitory, there is also elongation of the vessels, which, in consequence, become tortuous and varicose.

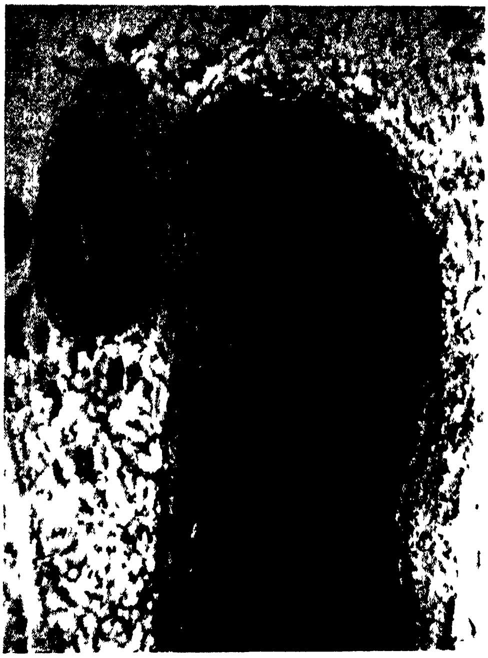

FIG. 290. *Thrombosis of large tributary of superior mesenteric vein* from same case as Figs. 408–9, pp. 739–40. The corresponding artery (on the left) is *not* occluded. Mallory's connective tissue stain × 15.

Causation. The occurrence of varicose veins in members of the same family for several generations, suggests that a predisposing cause may be some congenital or inherited weakness of the walls and the valves of the veins. Vitamin - deficiencies and endocrine disturbances are regarded by certain writers as accessory causal factors. After considering carefully the evidence in favour of these views, there seems little doubt that mechanical increase in blood-pressure within the veins themselves, such as occurs in central obstruction to the venous return, as in mitral stenosis or emphysema, is the most important direct or exciting cause. Obstruction to the portal circulation by tumours, cirrhosis of the liver, or other causes, may, singly or in combination, give rise to distension and varicosity of the veins of the rectum and of those at the lower end of the œsophagus. Pressure due to tumours, repeated pregnancies, etc., upon the veins returning blood from the lower limbs, may give rise to varicosity of the veins of the lower limbs. These causes are probably in themselves sufficient to produce this condition ; but they are, no doubt, aided by weakening of the walls of the vessels, absence or diminution of the external support of the surrounding tissues, and cardiac conditions in which the circulation is impeded. Gravity plays some part in the process, as is evidenced by the frequent occurrence of varicose veins in the legs of those whose occupation entails much standing.

Pathological Anatomy. The dilatation and varicosity of the veins are accompanied by thickening of their walls, and usually by incompetence of the valves—this incompetence in turn increasing the dilatation and the varicosity. The thickening of the walls of the veins affects especially the inner coat, which sometimes becomes calcified. Degenerative changes take place in the muscular coat, and calcification may also occur in it. The outer coat may show proliferative changes. Thrombosis is liable to occur in the dilated veins, and thrombi so formed may undergo organisation, or they may become calcified, leading to the production of **phleboliths** or " vein-stones " ; or they may become detached, in whole or in part, and give rise to embolism. The separation of the thrombi, with the formation of emboli, is more likely to occur in cases in which septic infection, with consequent softening, takes place. The tissue round the diseased veins may show chronic inflammatory changes. Thus are to be explained the chronic eczematous condition of the skin and the thickening of the subcutaneous tissue so frequently associated with varicose veins. On the other hand, the pressure of the dilated vessels often causes atrophy of the surrounding parts. Ulceration of the overlying skin and other tissues may occur, and ulcers so produced are usually " indolent " in character and, if untreated, persist for years and may lead to chronic thickening of the tissues, including even the bones, *e.g.*, the subjacent tibia in the case of the lower limb. The vein may rupture or be opened into by ulceration, and serious hæmorrhage be produced. This hæmorrhage, caused either by ulceration or rupture, is perhaps commonest from the varicose veins—hæmorrhoids—of the lower parts of the rectum : or, less frequently, from those at the lower end of the œsophagus in cases of cirrhosis of the liver.

Situations in which varicose veins most commonly occur :—

1. The veins of the lower limbs, especially in the long saphenous vein.

2. The veins of the lower part of the rectum and anal canal, immediately under the mucous membrane (pp. 739–741). These veins communicate with the inferior mesenteric vein—a tributary of the portal vein—and with the internal iliacs—tributaries of the vena cava. Thus, any obstruction to the portal circulation or any abnormal pressure in the intestines or in the abdominal cavity may cause dilatation of the venous plexus. The veins become varicose ; and bluish knots, varying in size, are seen pushing the mucous membrane before them. The varicosity is more liable to occur in these veins than in those of the limbs, because of the absence of valves in the veins of the portal circulation. These **hæmorrhoids** or **piles** may rupture ; thrombus-formation may take place in them ; and chronic inflammatory changes occur around them.

3. The veins of the spermatic cord. Dilatation and varicosity of the pampiniform plexus and the testicular vein formed from it—**varicocele**—occur especially on the **left** side, due, no doubt, to the longer course of the left testicular vein, as well as to the fact that it joins the left renal vein more or less at right angles. The protective valve usually present near its termination is sometimes absent.

4. The veins of the neck of the bladder and prostate in the male, and of the vagina and broad ligament in the female ; and those of the dura mater and of the lower end of the œsophagus, may be the seat of varices.

PHLEBITIS OR INFLAMMATION OF VEINS. This condition is liable to occur in veins which are dilated and varicose. It may spread from neighbouring inflammatory foci, such as infected wounds, erysipelas, etc., as in the thrombosis of the transverse sinus, secondary to suppurative middle-ear disease.

Microscopically, in such acute cases as arise by spread from neighbouring inflammatory areas, there is found an invasion of the various coats of the vein by inflammatory cells. Thrombosis frequently occurs, and the thrombi thus formed may become infected, and may soften, break down, and form emboli. In a second group of cases, the inflammation starts from within, and is most commonly the result of septic infection. Septic matter is introduced into the vein and induces thrombosis. This septic thrombus, however produced, acts as an irritant to the inner coat of the vessel, and causes an emigration of leucocytes, which infiltrate the various coats of the vessel—the thrombus eventually breaking down, and the vessel becoming filled with purulent material ("thrombo-phlebitis purulenta"). This septic exudate, which is distributed by the blood-stream and becomes lodged in various situations, causes multiple abscess-formation and pyæmia.

Non-septic phlebitis is frequently associated with thrombosis, and has been called "thrombo-phlebitis." It may arise as a result of injury to the vessel-wall, or it may be induced artificially by the injection of quinine and urethane or other chemical substances, as a therapeutic measure in the treatment of varicose veins. The thrombus so formed undergoes organisation, in whole or in part, and may become calcified, or be partially absorbed, leaving a thickening of the wall of the vein, especially of its inner coat. There may, however, be, in addition, some proliferation of the connective-tissue cells of the media. A similar condition which has been called "phlebo-sclerosis" is said to occur particularly in cases of syphilis and gout.

Thrombosis in veins is described on pp. 165–6.

DEGENERATIONS. Fatty and waxy or amyloid degenerations are not uncommon, and the changes in the veins due to these conditions are described on pp. 194 and 208 *et seq.*

Reference has already been made to Calcification (pp. 238 and 499–500).

GRANULOMATA. Tuberculous disease in any organ may spread so as to involve the veins, and, by destruction of the walls of these, the tuberculous material reaches, and is distributed by, the blood-stream, giving rise to general tuberculosis. Sometimes ulcerative patches containing large numbers of bacilli are found in the walls of the veins themselves.

Syphilis produces, as a rule, much less evident results in veins than in arteries. Definite histological changes in the veins are uncommon, but gummatous infiltration and syphilitic endophlebitis occur, as does also the condition of syphilitic periphlebitis, which is occasionally nodose in its distribution (*cf.* p. 479 *et seq.*, for the analogous lesions of arteries).

TUMOURS. Of **primary** tumours, myomas and sarcomas have been described, but are very rare. Tumours of various kinds involve the walls of the veins **secondarily,** and may spread along their lumen. Invasion of tributaries of the pulmonary veins by bronchial carcinoma (pp. 574 and 1144–50), as well as by secondary malignant growths in the lungs, is a common method of the further dissemination of these tumours by the blood-stream, by which they may reach the brain and elsewhere.

CHAPTER XVII

DISEASES OF THE RESPIRATORY SYSTEM

SECTION I

DISEASES OF THE NASAL CAVITIES AND NASO-PHARYNX[1]

CONGENITAL ABNORMALITIES. Complete absence of the nose, absence of the septum, and stenosis of the orifices, are very rare defects. Defects, due to involvement of the nasal cavities in the conditions of hare-lip and cleft-palate, are comparatively common (p. 702); deviation of the septum is common (*see* opposite, under " Chronic Catarrh ").

DISTURBANCES OF THE CIRCULATION. Hæmorrhage from the nose, **epistaxis,** may occur without any apparent cause, or it may result from the rupture of over-distended vessels in acute congestion or in chronic venous congestion of the mucous membrane. It occurs frequently in leukæmia and hæmophilia, and in other disorders in which the blood-vessels are diseased, or the blood-pressure is unduly high, especially in some forms of nephritis. It is not uncommon at the onset of typhoid fever and other infectious diseases. A certain amount of blood is often mixed with the purulent discharge of rhinitis or from an ulcerated diphtheritic throat, or with the exudate from inflammatory conditions of the accessory sinuses.

CEREBROSPINAL RHINORRHŒA (p. 965). The discharge of cerebrospinal fluid from the nose may be due to fractures of the base of the skull; may complicate operations on the nasal sinuses; or result from injuries to the frontal or ethmoidal sinuses. Sometimes, however, the discharge seems to be independent of any trauma or any congenital defect, and it has been suggested that such spontaneous discharge may be due to leakage along the sheaths of the olfactory nerves.

INFLAMMATION :—

(*a*) **Acute Catarrh**[2] is a common symptom in many infective diseases such as scarlet fever, diphtheria, hay-fever, influenza and measles ; but its most typical manifestation is seen in **Coryza**[2]—the ordinary " common cold," in which the mucous membrane is at first red and dry, and the vessels are dilated. This condition is followed rapidly by exudation of lymph with migration of leucocytes from the distended vessels ; and there is a discharge from the nose, at first mucoid, later serous, and then mucopurulent. The associated organisms are the potential pathogens of the upper air-passages, and there may be a considerable increase in the number of these. Coryza (p. 121) is now generally regarded as an infection produced by a virus allied to that of influenza (p. 120) ; and it has been shown experimentally that bacteria-free filtrates from the secretion in acute cases produce the characteristic symptoms of the disease on inoculation in chimpanzees and in man. In the acute catarrh (**acute rhinitis**) of measles and influenza, a virus is probably the causal factor ; but in scarlet fever and diphtheria the lesions are bacterial in origin. In the two latter diseases, a definite " false " membrane is formed on the tonsils. This membrane may be merely an exudate composed of fibrin, leucocytes and desquamated epithelial cells ; or, as is common in diphtheria, there may be, in addition, necrosis of the epithelial and subepithelial tissues. Such false membrane is of a dull greyish or pale-yellowish colour—like " wash-leather " in appearance—and can be detached only with some difficulty, leaving a raw, bleeding surface.

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[1] *See also* Diseases of the Soft Palate, Pharynx and Tonsils, p. 708 *et seq.*

[2] *Catarrh* and *coryza* : for origins of these words, *see* footnote on p. 41.

The posterior nares and especially the naso-pharynx are important areas for the lodgment of bacteria, and the naso-pharynx is a common position in which meningococci are found in carriers, as well as in otherwise healthy contacts and in patients actually suffering from cerebrospinal fever (p. 981). Adenoids, and abnormalities such as thickening and deformity of the septum, enlargement or deformity of the middle turbinates and narrowness of the nasal passages, associated with some œdema of the mucosa, are frequently found in meningococcal carriers. In poliomyelitis (p. 105), the virus is present, especially in the naso-pharynx.

Adenoids. Hyperplasia of the lymphatic tissue, giving rise to " adenoids," is common in children, and, as already noted, is an important factor in producing carriers in cases of infection with meningococci (*Neisseria meningitidis*). Other bacteria may also be arrested in these masses of lymphoid tissue, and adenoids may be a point of entrance of tuberculosis—the bacilli, air-borne or in milk, becoming lodged in this tissue.

(*b*) **Chronic Catarrh.** This is a sequel of repeated acute attacks, and also occurs particularly in syphilitic and in tuberculous subjects. Narrowing of the nasal passages, especially when due to, or associated with, deviation of the septum, is an important predisposing causal factor ; and vitamin-deficiency, particularly of vitamin A (p. 439), produces changes in the tissues which render them more susceptible to chronic catarrhal infection. The mucous membrane becomes thickened, especially over the inferior turbinate bones ; and, in some cases, polypi are formed. This " hypertrophic " (better termed " hyperplastic ") rhinitis tends to persist, and frequently is followed by **atrophic** changes ; dry crusts are formed, and extensive ulceration results. The discharge becomes purulent and, because of its offensive odour, to this atrophic variety of rhinitis the term **ozæna** [1] is applied. In both acute and chronic catarrh of the nasal passages, **involvement of the para-nasal sinuses** is a common and important complication.

Tuberculosis (p. 56) **and Syphilis** (p. 87).

TUMOURS. Mucous and fibrous polypi are sometimes described as " tumours," but many of the so-called " nasal polypi " are really composed of inflamed and hyperplastic mucous membrane and are not true neoplasms. Papillomas, sarcomas, and both squamous epitheliomas and glandular carcinomas, as well as many mixed tumours, occur.

FOREIGN BODIES in the nose may become encrusted with lime-salts and form nasal calculi or rhinoliths.

PARASITES. Certain fungi, *e.g.*, *Aspergillus fumigatus* (pp. 94 and 568A *Rhinosporidium seeberi* (pp. 95 and 382) : and maggots or the larvæ of flies (p. 432) occasionally attack the nasal passages.

(**Pharynx.** Diseases of the pharynx are described under the Digestive System, p. 708.)

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[1] *ὄζαινα*, *ozaina*, a fœtid condition of the nose, from *ὄζειν*, *ozein*, to have a smell, *cf.*, *ὄζων*, *ozōn*, smelling, *i.e.*, having a smell.

SECTION II

DISEASES OF THE LARYNX, TRACHEA AND BRONCHI

Malformations are rare.

Disturbances of the Circulation. Active hyperæmia, acute and chronic venous congestion, and hæmorrhages do not present any special features calling for separate description.

Foreign bodies, such as particles of food, fish- or meat-bones, coins, buttons, teeth, may gain access to the upper air-passages, obstruct the orifice of the glottis, or, if they become impacted, produce dyspnœa and spasm, and, if the patient survives, subsequent inflammatory changes.

INFLAMMATION. (*a*) **Acute catarrh** of the larynx occurs as a result of chemical or mechanical irritation, or may be caused by bacterial or other irritants, as, for example, the catarrh which sometimes arises during an attack of measles, whooping-cough, smallpox, influenza, or typhoid fever. Most commonly, it is an extension or complication of catarrhal inflammation of the throat, trachea, or bronchi. The exudate, which is generally scanty, is at first mucoid, and later contains numerous pus- and catarrhal cells. The mucous membrane is red and swollen, though the swelling may be slight, and usually causes no obstruction. The suffocative attacks which sometimes occur in children with acute laryngitis are due to reflex spasm of the muscles of the glottis, as well as to œdema of the neighbouring soft parts.

(*b*) **Chronic catarrh** may follow the acute form, or it may occur independently of it. Over-use of the voice, and exposure to cold, or to irritating vapours or dust, are among the predisposing causes which damage the tissues and allow bacterial invasion. The mucous membrane is thickened and its surface appears granular, probably the result of swelling and proliferation of lymphoid tissue. Small hæmatomas may develop beneath the mucosa of the vocal folds (pp. 568A–569). These subsequently organise, and produce one of the forms of "speaker's nodule." Flat superficial, or crater-like ulcers are found in the region of the posterior commissure, or in the epiglottis and the ary-epiglottic folds. **Microscopically,** the mucous membrane shows overgrowth of connective tissue. The contraction of this, and the later atrophic changes, may bring about stenosis of the larynx—a lesion seen especially in syphilitic disease.

(*c*) **Œdema Glottidis.** In this condition, there is great swelling of the tissues of the glottis and its neighbourhood, with œdematous infiltration, especially of the looser structures—the whole of the mucous and submucous tissues being involved. As already stated, the œdema may occur during the course of disease of the kidneys, or in so-called angio-neurotic cases (which are probably toxic or allergic in origin), and also occasionally as the result of idiosyncrasy to certain drugs and foods ; but it is associated as a rule with acute or chronic inflammatory affections of the larynx. Thus, it may occur during an acute catarrhal inflammation, or in connection with diphtheria, the pustular stage of smallpox, typhoid fever, measles, scarlet fever, and in syphilis or tuberculosis ; or it may be brought about by the spread of inflammation from adjacent parts, or by the direct action of an irritant, as, for example, the œdema which results from a scald produced by drinking boiling water : or from the action of a strong mineral acid, etc. The parts especially affected are the looser submucous tissues of the ary-epiglottic folds, the ventricular bands, and, to a somewhat less extent, the epiglottis, especially at its base. Sometimes, particularly if the irritant be a septic one, the œdematous infiltration is semi-purulent or purulent, and may extend along the submucous tissue of the trachea for some distance below the glottis. This is seen in Ludwig's angina (p. 711).

(*d*) **Perichondritis.** Inflammation of the perichondrium may be more or less chronic and give rise to mere induration and swelling; but, more often, pus is formed under the perichondrium. This accumulation of pus cuts off the cartilage from its blood-supply, and is generally followed by necrosis. The cricoid cartilage is most frequently affected, but the inflammatory reaction, especially when suppuration has occurred, may extend widely. Perichondritis is commonly a secondary result of tuberculosis or of syphilis of the larynx, but may supervene in cases of typhoid fever, the lesion then being situated towards the base of the arytenoid cartilages close to the posterior commissure.

(*e*) **"Membranous" Laryngitis.** In this condition, the larynx at first shows hyperæmia and increased mucous secretion. This is succeeded by the formation of a more or less adherent greyish or yellowish "membrane" which, on **microscopical examination,** is found to consist largely of fibrin and entangled leucocytes, with also some degenerated and degenerating cells of other varieties. In the majority of cases, this **false membrane** is diphtheritic in origin, and, scattered through it, may be found the Klebs-Lœffler bacillus in association with other organisms, especially staphylococci and streptococci, but a "membrane," similar in nature, may be produced in scarlet and typhoid fevers and other infectious diseases, and also as a result of violent irritation, such as might be caused by the inhalation of steam. A varying degree of necrosis of the mucous membrane—especially in its more superficial layers—is also present.

Tuberculosis and Syphilis (*see under* "Granulomata," pp. 56–7 and 77: and 87).

Tumours of the Larynx (*see under* "Tumours of the Air-Passages," p. 568A *et seq.*).

DISEASES OF THE TRACHEA

Circulatory disturbances, similar to those seen in the larynx, to which reference has already been made, may affect the trachea.

Compression by aneurysms, or mediastinal growths, may take place; and, as a result of the erosion by an aneurysm, or the necrosis and suppuration produced by breaking-down lymph-nodes, perforation may supervene.

Inflammatory lesions are generally the result of the extension of a laryngitis or a bronchitis, and show much the same features as are observed in the larynx or in the bronchi. In influenza, tracheitis is a conspicuous symptom (p. 120, and Figs, 291 and 292, p. 506).

ANTHRAX.[1] In this disease, the infection in the lung is due to the inhalation into the bronchial passages of the spores of the causal organism (*Bacillus anthracis*) in wool or hairs from infected animals and there producing **"Woolsorters' disease,"** the pathology of which was first elucidated by the late Professor W. S. Greenfield in a series of papers published in 1880–82 in the *Proceedings of the Royal Society* and elsewhere, and in the *Annual Reports of the Medical Officer of the Local Government Board.*[2] The lesion consists of swollen

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[1] Greek. ἄνθραξ, ἄνθρᾰκος, *anthrax*, *anthrăcos*, charcoal, coal, hence a dark-coloured stone, a ruby or carbuncle, and secondarily, a malignant pustule; also Latin, *anthrax*, *anthrăcis*, coal, hence something coal-black or very dark in colour.

[2] For the year 1880, Appendix A, No. 8, page 66: and for the year 1881 ("Supplementary Report on the Woolsorters' Disease in the Bradford District"), Appendix B, No. 3, page 207.

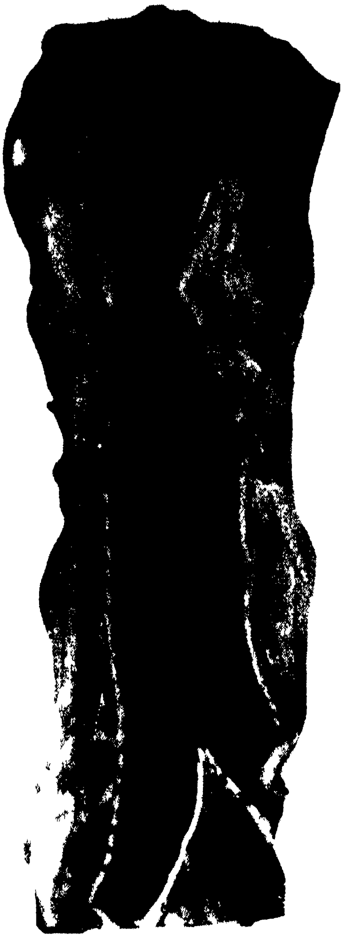

FIG 291 *Trachea from a case of influenza* There was marked tracheitis with hæmorrhages (the small black spots)

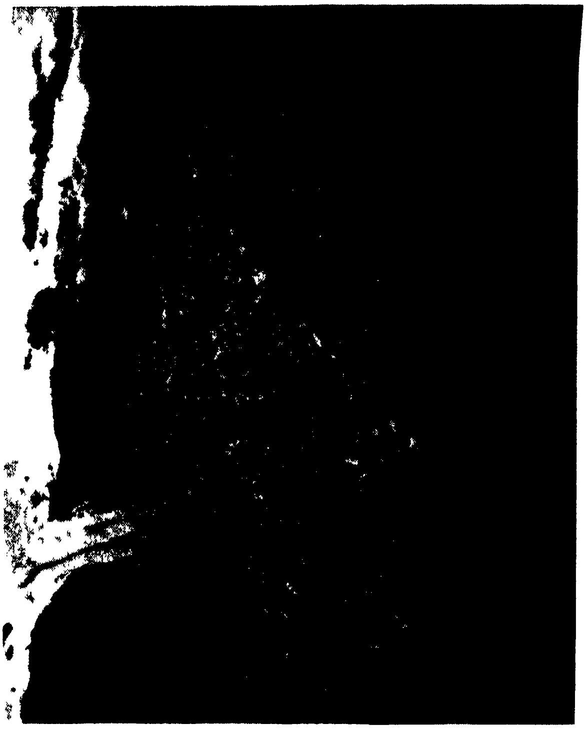

FIG 292 *Section of trachea in a case of influenza,* showing intense congestion in the submucous tissue and, at the left margin of the section, necrosis of the mucous membrane, towards the lower part of which is seen the opening of a mucous gland × 75

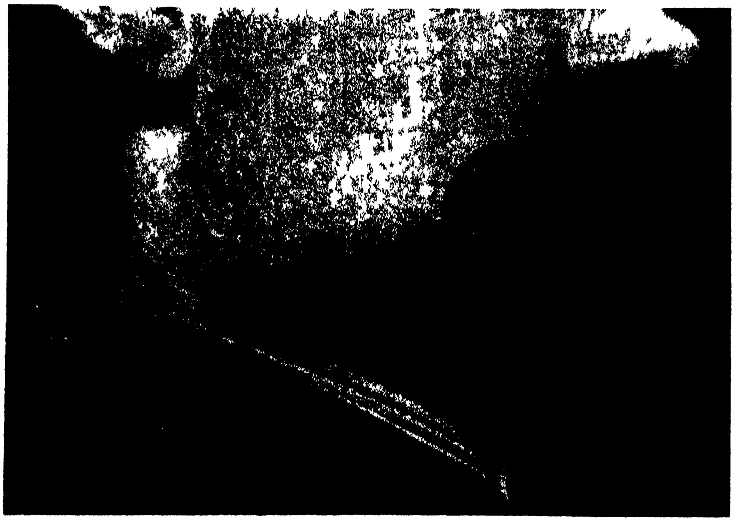

FIG. 293. *Malignant pustule on the face,* showing central "black" eschar and ring of vesicles The patient was a butcher (Sir Harold Stiles and Carnegie Dickson's case, R I E.)

patches, often with considerable hæmorrhage into them, in the mucous membrane in the lower part of the trachea and the larger bronchi. The tissues are inflamed and œdematous, and ulceration may be present. Associated enlargement of the mediastinal and bronchial lymph-nodes, hæmorrhagic infiltration of the cellular tissues of the region, pericardial and pleural effusions, hæmorrhages into the serous membranes and subserous tissue, and congestion, collapse, and œdema of the lungs, are constant features. The bacilli are present in large numbers.

The ordinary method of infection in **cutaneous anthrax** is by the invasion of an abraided surface of skin of the face, hands, forearms, shoulders or back in workers, from contact with infected hides or hair. Infection may take place also from the use of cheap shaving-brushes made, for example, in Japan, from infected and inadequately sterilised bristles. In the skin, the first indication of the primary local lesion is the development of a small red pimple, which soon becomes a vesicle containing clear or blood-stained fluid, and surrounded by an area of intense congestion. Central necrosis occurs, and, eventually, a dark-red or " black " eschar, surrounded by a ring of vesicles (Fig. 293 on p. 506). From this primary lesion—the so-called "**malignant pustule**"—subcutaneous œdema spreads, especially along the lymphatic vessels ; and the neighbouring lymph-nodes become inflamed. The characteristic bacilli are found in the vesicles, and may invade the blood-stream. In other instances, the intestine is infected by ingestion of spores—the local lesion being usually in the jejunum. The mucosa becomes infiltrated and œdematous, and ulceration may occur. The mesenteric lymph-nodes become swollen, œdematous and hæmorrhagic. A secondary hæmorrhagic meningitis is occasionally found (p. 974).

Tuberculosis and **Syphilis** of the trachea occur under the same conditions as in the larynx and bronchi (pp. 77 and 87), and produce lesions with much the same characters.

DISEASES OF THE BRONCHI

In studying the diseases of the bronchi, it is essential to recall some of the more important points in connection with the anatomical distribution and the histological structure of these tubes. Recent work on the former of these subjects has not yet found its way into the anatomical textbooks, and a useful introduction to the "*Anatomy of the Bronchial Tree,*" by J. Hardie Neil, W. Gilmour and F. J. Gwynne, of Auckland, New Zealand, will be found in the *British Medical Journal,* 1942, **ii,** 495. In this article, the more or less constant distribution of the bronchi within the lungs **in twelve segmental zones** is emphasised, and these are enumerated as follows :—

Upper Lobe :—

1. Subapical.
2. Apical.
3. Axillary.
4. Anterior.

Middle Lobe :

5. Anterior.
6. Axillary.

Lower Lobe :—

7. Apical.
8. Cardiac.
9. Subapical.
10. Anterior Basal.
11. Axillary Basal.
12. Posterior Basal.

A knowledge of these "**segments**" or "**zones,**" each forming separate "**respiratory districts,**" supplied by sub-lobar groups of bronchi with a "territorial distribution," is of importance to physician and surgeon and to the pathologist, in relation to the occurrence within the lungs of lesions such as bronchiectasis, tuberculosis or bronchial carcinoma.

The mucous membrane of the bronchi is lined by a layer of columnar ciliated epithelium, beneath which there is a translucent homogeneous basement-membrane. Between the basement-membrane and the muscular coat, there is a layer of vascular connective tissue containing elastic fibres and masses of lymphoid tissue. The muscular coat or bronchial muscle (muscularis mucosæ), which is really the deeper part of the mucosa, consists mainly of circular, together with a few longitudinal, muscle-fibres. External to the muscularis mucosæ is the adventitial coat, composed of loosely arranged connective tissue, which is continuous with the interstitial connective tissue of the lung. In this adventitial coat, the mucous glands and the cartilages are situated. In the smaller divisions of the intrapulmonary bronchi, the adenoid tissue becomes gradually reduced in amount until, in the minute branches, no trace of it can be found. Similarly, the cartilages become irregular and smaller, and finally disappear. On the other hand, the muscularis mucosæ becomes thicker. The epithelium also alters in character, becoming more cubical, or even flattened in the terminal branches. On this difference in histological structure depend, to a certain extent, the variations in the character of the lesions which are found in different parts of the bronchial tree, even although these may in each case be produced by the same irritant. Thus, diseases of the larger bronchi resemble those of the trachea with which their structure closely corresponds, and these lesions do not tend to spread to the adjacent lung-tissue; whereas affections of the minute or capillary bronchi are more closely allied to those of the lung-parenchyma, and tend to spread to it.

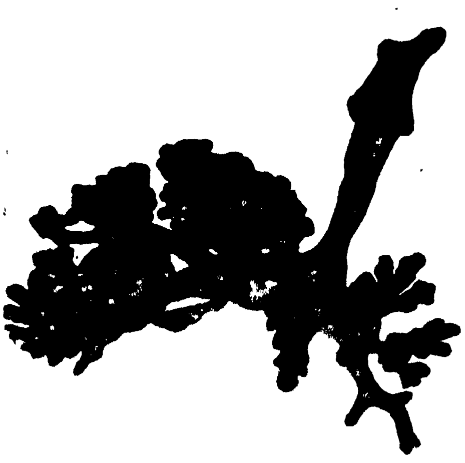

FIG. 294. "*Fusible-metal*" *cast of bronchioles with the infundibular passages, etc.*, showing the saccular appearance of the terminal vesicles or infundibula. (Made by Chas. W. Cathcart, C.B.E., F.R.C.S.E.) × 7.

INFLAMMATION. Inflammatory changes in the bronchi vary much in intensity. In the slighter forms, the larger and medium-sized tubes mainly are affected. Where the minuter divisions of the bronchial tree are inflamed, the condition is generally, if not always, associated with accompanying disease of the lung-parenchyma. Thus, in describing **bronchial catarrh** or **bronchitis,** it is convenient to limit the description to inflammatory changes in the larger and medium-sized bronchi, leaving the changes in the smaller branches to be dealt with under **bronchopneumonia.**

1. **ACUTE BRONCHITIS OR BRONCHIAL CATARRH.** This condition, when not associated with inflammation of the lung-parenchyma, is confined mainly to the medium-sized intra-pulmonary bronchi; and may arise from exposure to cold, the inhalation of irritant vapours, or by extension from a pharyngitis, laryngitis or tracheitis. The condition commonly is associated with infectious fevers. The organisms most frequently present are streptococci, pneumococci, Pfeiffer's bacillus and some of the ordinary commensals of the naso-pharynx.

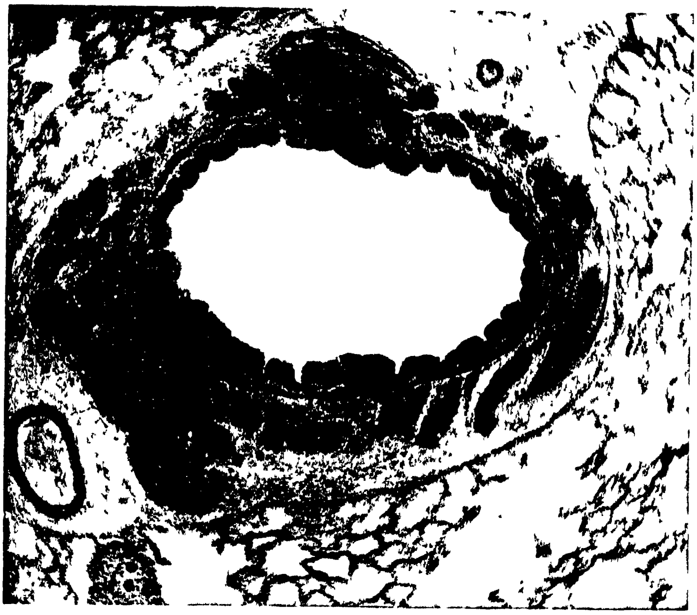

FIG. 295. *Transverse section of a normal bronchus*, showing the various structures mentioned in the text. × 30.

The mucous membrane is swollen, and intensely red. In the early stage, the membrane may be dry, but, later, it becomes covered by a mucoid, mucopurulent, or a purulent exudate. This exudate is at first viscid, tough, and more or less translucent, and composed largely of mucin which is poured out in excessive amount from the inflamed mucous

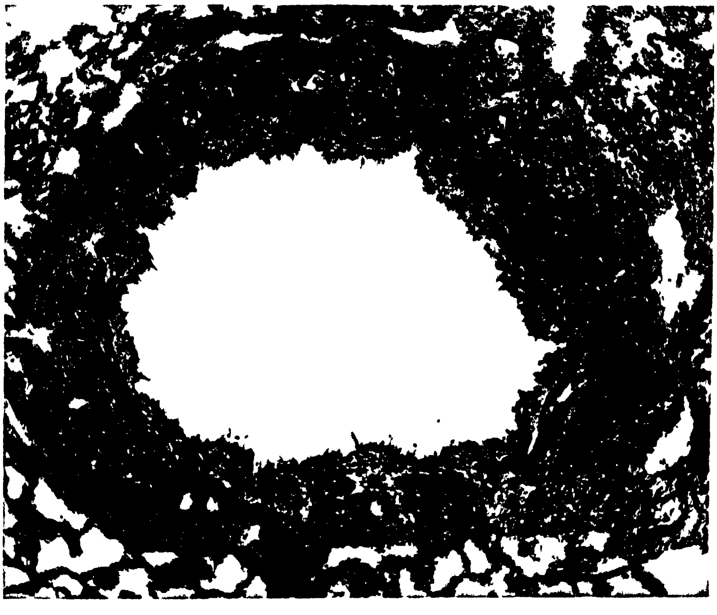

FIG. 296. *Transverse section of a bronchus in a case of acute bronchitis.* Compare with Fig. 295, above, and note here the infiltration of the mucosa with inflammatory cells, the separation and swelling of the muscularis mucosæ, swelling of the basement-membrane, and the irregular appearance of the lining-cells. × 45.

glands. In the later stages, it becomes less tough, more opaque, and yellowish-white or greenish in colour, owing to the infiltration of the mucin with the cellular and fluid products of the inflammatory process. Usually, the cellular content, in the early stages, is not high, and consists mainly of leucocytes, red corpuscles and a few cylindrical or tailed and often ciliated epithelial cells. There may be some mononucleated cells from the bronchi derived probably from lymphoid tissue along the tract. Later, when the mucopurulent stage is reached, the polymorphonuclear and mononuclear leucocytes are greatly increased in numbers, and the epithelial cells have lost their shape and show various degenerations, and may be shed in irregular masses into the lumen. The basement-membrane shows irregular swelling; the mucosa becomes infiltrated with leucocytes, and its fibres and the fibres of the muscularis mucosæ are separated from one another and swollen by the accumulation and imbibition of the transuded lymph. The mucous glands show catarrhal changes.

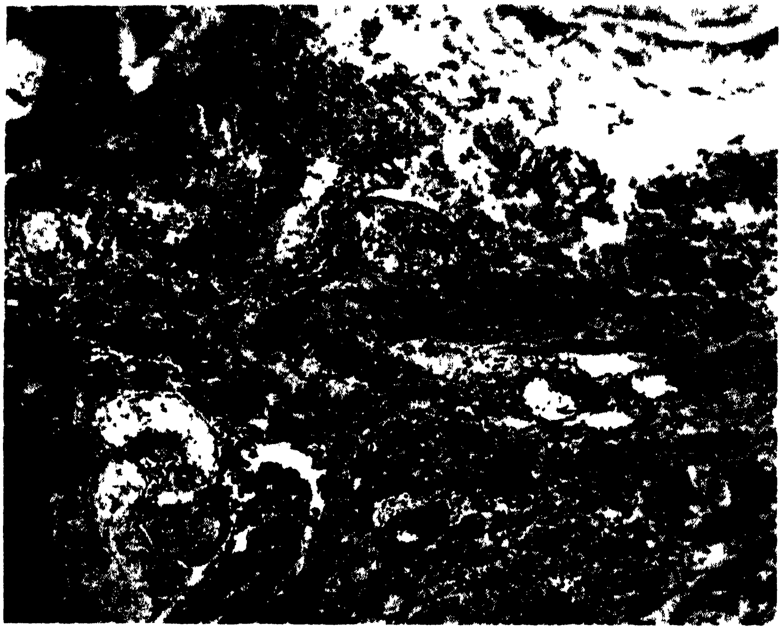

FIG. 297. *Acute bronchitis*, showing dilated vessels (dark areas), swollen basement-membrane, infiltration of submucous tissue with leucocytes, shedding of the epithelial lining-cells into the lumen and the presence in the lumen of emigrated leucocytes. × 75.

2. **CHRONIC BRONCHITIS** occurs after repeated acute attacks, especially in persons who have some co-existing or intercurrent affection of the heart or lungs which maintains a congestion of the mucous membrane. The membrane often shows a brownish-red, or even a slaty-blue, pigmentation. The lumen of the bronchus is sometimes dilated, and its normal corrugated appearance to a large extent lost. Later in the disease, the mucous membrane becomes thinned and atrophied, the fibrous and cartilaginous framework of the bronchus becoming more apparent. Minute ulcers, just visible to the naked eye, are sometimes seen between the cartilage-rings. Microscopically, the

epithelial changes are very pronounced, almost the whole of the ciliated cells having disappeared. The latter may, in parts, be replaced by columnar or polygonal epithelium, and occasionally even undergo metaplasia to squamous cells which are patchy or sometimes diffuse in their distribution. The basement-membrane shows irregular thickening. The submucosa may show considerable swelling, the vessels be much dilated, and the mucous glands in a condition of chronic catarrh and atrophy, some of them becoming cystic from obstruction of their ducts. The mucosa is infiltrated with cells, mostly of the mononucleated type, and presents the appearance of vascular granulation-tissue. At a later stage, the loose vascular structure of the mucosa may be replaced by well-formed fibrous tissue, which spreads to the lung-parenchyma. The cartilages undergo degenerative changes and partial absorption, whilst the muscular tissue becomes infiltrated with inflammatory cells, and may atrophy and be replaced by fibrous tissue. The bacteria associated with this condition are the same as those found in acute cases. The exudate is often abundant and frequently purulent. It may be pigmented from the presence of carbon-particles or of altered blood. Sometimes, especially in subacute cases, the sputum is tenacious, viscid and scanty. Where the bronchitis is associated with emphysema, the sputum varies considerably in quantity, and may consist of gelatinous or frothy mucus, or yellowish-white mucopurulent exudate, often tinged with blood. It usually contains pus-cells and may show red corpuscles and pigmented cells derived from the lining-membrane of the alveoli. Occasionally, eosinophil cells are found, but these are more characteristic of cases of asthma.

3. **MEMBRANOUS OR PLASTIC BRONCHITIS.** This condition is characterised by spasmodic attacks of coughing, which come on suddenly, and during which casts of portions of the bronchial tree are expectorated. The attacks are often preceded by hæmorrhage. These casts are whitish or greyish-white in colour, and branches, corresponding to the divisions of the bronchi, are seen if the cast is floated out in water. The mode of their formation is unknown. They are generally regarded as being composed of masses of fibrin, and hence the condition has been called "**fibrinous bronchitis.**" In some cases, however, the cast is composed mainly of masses of epithelial cells, with little or no fibrin. Similar casts, which are definitely fibrinous in character, are sometimes formed in the bronchial tubes in cases of diphtheria ; and, in acute pneumonia, a fibrinous exudate may be produced in the smaller bronchi, giving rise to casts, which may be expectorated.

STENOSIS AND DILATATION :—

Stenosis and obstruction of the bronchi may be caused from without by the pressure of tumours or aneurysms. Tumours of the mediastinum may extend along the bronchi, compress and invade their walls, and thus cause considerable narrowing or even complete obstruction. Tumours of the bronchial wall itself, syphilitic infiltration of it, foreign bodies, plugs of tenacious mucus or fibrinous material, especially in the minute bronchioles, may cause obstruction, with collapse of corresponding portions of the lung-tissue.

Bronchiectasis or Dilatation of the Bronchi. Dilatation ot fhe bronchi is of two main types—**saccular** and **cylindrical** or **digitate**. The latter occurs, as a rule, early in life and may result from forced inspiratory efforts which accompany or follow prolonged paroxysms of coughing during whooping-cough or the bronchitis often associated with measles or other diseases. If weakening of the walls of the bronchi from any cause is present, or if, by any obstruction, the expansion of the lung is impeded, the forced inspiratory effort will be more potent in causing the bronchial dilatation. In the saccular variety, the weakened and dilated segments in the bronchi are more localised and the increase of fibrous tissue greater than in the cylindrical form. The weakening of the walls may be due to a congenital deficiency in the muscle-bundles, but more commonly it is the sequel of inflammatory and catarrhal changes in the bronchus and the surrounding tissues. The mixture of secretion and exudate in such bronchiectatic cavities tends to accumulate and to become invaded by organisms of putrefaction, with further weakening and progressive dilatation of the walls. Sometimes, localised dilatations are the result of inflammatory changes and retention of secretion in the neighbourhood of a foreign body, such as a tooth or tooth-fragment inhaled during extraction under anæsthesia. In cases of pulmonary fibrosis, the contraction and condensation of the lung leads to what may be regarded as a " compensatory " dilatation of the air-passages in order to accommodate the excess of air. In addition, the actual contraction and dragging of the fibrous tissue aids in dilatation, particularly if the pleura is thickened and adherent to the chest-wall, for, in such cases, the bands of fibrous tissue extending between the pleura and the bronchi, as they undergo gradual contraction, pull the bronchial walls towards the fixed pleura. In chronic phthisis, the combined effects of the weakening of the walls of the bronchi and of their surrounding tissues by the invasion and ulceration of the tuberculous infection, the accumulation of retained secretion and exudate, the intra-pulmonary pressure due to coughing, and the dragging on the walls of the bronchi by the newly formed fibrous tissue, all combine to produce an irregular bronchial dilatation. In **congenital atelectasis** (p. 522), a condition in which portions of the lung do not expand at birth, bronchiectasis may occur, because the bronchial walls are not so well developed as in the normal lung, and because the bronchi by their dilatation tend to " compensate " for the failure of the alveoli to expand, since the total volume tends to approximate to that of the hemi-thorax to which the lung must adjust itself.

Obstruction of the larger bronchi may result from the cicatricial contraction of syphilitic lesions, especially those occurring at the bifurcation of the trachea, or from the pressure of aneurysms of the aorta or tumours, or by the lodgment of foreign bodies. If the obstruction is complete, pulmonary collapse will follow. Usually, however, the obstruction is at first partial, with resulting retention of secretion, weakening of the bronchial walls, and dilatation. Infection with bacteria is liable to produce purulent bronchitis and bronchopneumonia. In bronchitis of the smaller tubes and in bronchopneumonia, dilatation is frequently seen, and is exaggerated in those cases in which resolution is delayed and incomplete, and especially if fibrosis of the lung-tissue has occurred.

Morbid Anatomy. The sacculated variety of bronchiectasis is seen especially in the various forms of tuberculosis, where local inflammatory and destructive processes are at work, but it is also a feature in silicosis and fibrotic conditions in general, though usually in less pronounced degree. The dilated

FIG. 299. *Lung.* Bronchiectasis in the lower lobe, resulting from pressure by a tumour on the branch of the bronchus of that lobe.

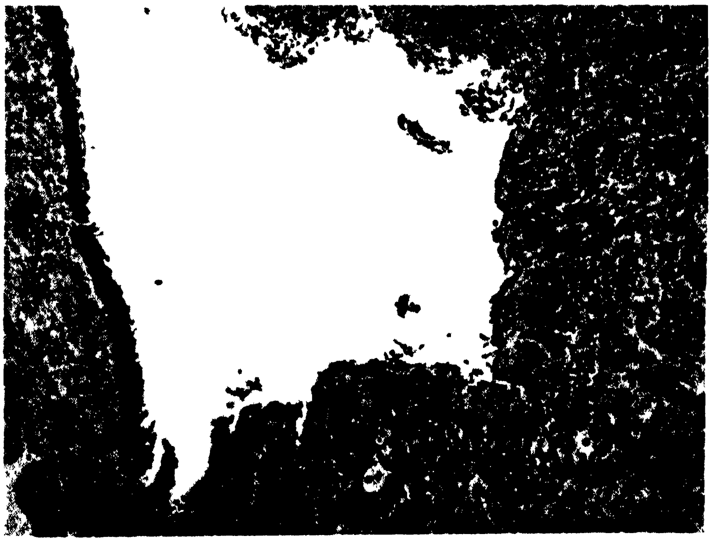

FIG. 300. *Lung.* Bronchiectasis, showing cavity lined by stratified epithelium. × 100.

tubes may assume the form of large, irregular cavities. These have usually a definite lining-membrane—which is often congested and covered with purulent exudate.

In the digitate or cylindrical form, the medium-sized bronchi, perhaps throughout a considerable part of the lung, are widened unduly, the cause being, as noted above, irritation such as chronic or repeated attacks of bronchitis. The dilatation may be regular; but, more commonly, the tubes show a diffuse, irregular sacculation. This digitate or cylindrical form is seen in the smaller bronchi in some cases of pneumonia.

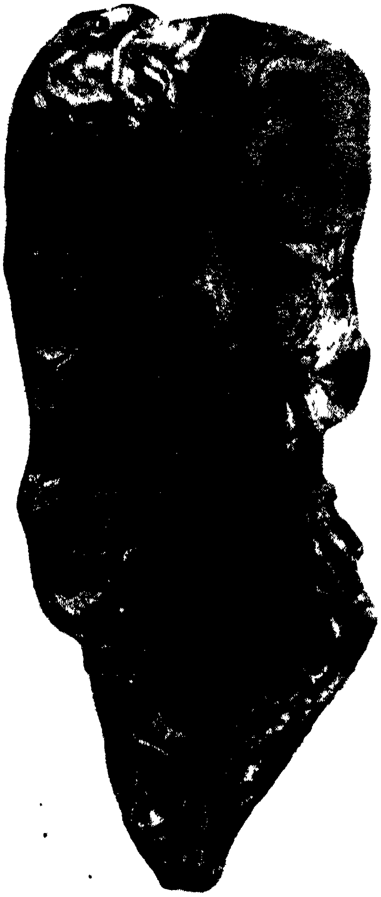

FIG. 301. *Congenital cystic disease of the lung.* Such cases have often in the past been regarded merely as "bronchiectatic." (By courtesy of Dr. Norah Schuster.)

Morbid Histology. The microscopical appearances of the dilated bronchi vary considerably, the variation depending, to a certain extent, on the exciting cause. If the inflammatory changes are pronounced, the tissues of the wall are infiltrated with inflammatory cells, and the normal structures are altered or destroyed; whilst, in other cases, the structures of the wall may be thinned and stretched, but still recognisable. The epithelium lining the cavity may be intact or destroyed, and the whole mucous membrane be replaced by granulation-tissue. The epithelium may undergo metaplastic changes and become cubical or squamous. The exudate—generally abundant—has a very fœtid odour. Usually it is greyish or greyish-brown in colour, liquid and purulent, though, in some cases, it is thick, viscid, and blood-stained. Pus-cells are found in considerable numbers; elastic tissue may be present when destruction of the walls is taking place; fatty-acid crystals, cholesterol- and hæmatoidin-crystals are sometimes found; and alveolar cells containing pigment, mucin or fatty débris, are present. Occasionally, calcium-salts are deposited, giving rise to the so-called "lung-stones." In addition to various pathogenic bacteria, putrefactive organisms are present in considerable numbers.

Congenital Cystic Disease of the Lung.[1] In addition to the dilatation of the bronchi which takes place in lungs which have only partially expanded at birth, a true congenital cystic condition is now recognised. Although it occurs occasionally in association with congenital cystic disease of other organs, it is found more commonly as a condition of the lung only. Such pulmonary cystic lesions are found in the fœtus ; they may show themselves at or soon after birth, or at any age later in life (for an analogous progressive development in later life of other "congenital" disorders and abnormalities, *see* pp. 1043 and 1069–70). The commonest form of the disease is a cystic dilatation of the bronchi which differs from acquired saccular bronchiectasis in that it is **developmental**, not degenerative, in origin, and tends to affect the upper and middle portions rather than the bases and lower parts of the lungs. Its presence *precedes* the occurrence of septic infection if and when the latter occurs ; and, histologically, microscopical examination indicates an abnormal growth of normal tissues—neighbouring and adjacent bronchi being approximately normal ; whilst in bronchiectasis they are deformed and dilated, and the changes in them are usually preceded or accompanied by septic infection, which, indeed, may be the direct cause of the bronchiectasis.

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[1] "Congenital Cystic Disease of the Lung," by T. Holmes Sellors, in *Tubercle, a Journal of Diseases of the Chest*, 1938, **20**, 1. "Discussion on Cystic Disease of the Lung," by W. Burton Wood, Holmes Sellors, Tudor Edwards and others, *Proceedings of the Royal Society of Medicine*, London, 1940, **33**, 335. From these papers the above description and classification of congenital cysts of the lung is mainly taken, and to them we refer our readers for further clinical and radiological details.

Various **types of congenital cyst** are described, and the classification has been founded chiefly upon their radiological appearances—large "**balloon-cysts,**" usually single : smaller "**solitary cysts,**" usually single, but sometimes more than one in a "lung-field" : "**bubble-cysts,**" in which the whole lung may appear to be replaced by a series of medium-sized cavities with "a curious resemblance to a picture of air-containing bowel," as shown in Fig. 301, which we owe to the kindness of Dr. Norah Schuster. Clusters of smaller cysts, sometimes confined to a single lobe, have been described as "**berry-cysts.**" These are spherical, and give a characteristic appearance radiologically with lipiodol. Some cysts are either originally, or become secondarily, filled with liquid, the so-called "**fluid-filled cysts.**" These different varieties of cyst all develop in connection with the bronchial tree, mostly communicate with the bronchi, and their walls exhibit a bronchial-wall-like structure with evidence of disorderly growth, not degeneration, resulting apparently "from failure of the extremely complicated system of lung-budding which should proceed until the final alveoli are formed. The budding stops prematurely, whether earlier or later, and the terminations of the already-formed bronchi apparently swell and thin out to occupy the spaces where pulmonary parenchyma should have developed, and dilated bronchi take the place of the lung alveoli" (W. Burton Wood, *loc. cit.*). Septic infection of the cysts does not invariably occur, but is a serious and sometimes rapidly fatal complication. Such cases may clinically be mistaken for pulmonary phthisis, acquired bronchiectasis or interlobar empyema. Bronchiectasis as a secondary complication from pressure of the cysts upon neighbouring bronchi, and pneumothorax from rupture of a cyst into the pleural cavity with resulting pyo-pneumothorax, are amongst the sequels of the disease. Surgical treatment of such cases has been successful if undertaken before septic infection has supervened.

ASTHMA

In asthma or, as it is frequently designated, **bronchial asthma,** there is, during the attack, a spasm of the smaller bronchi, and, in some cases, the smaller tubes show a definite increase of muscle, and inflammatory changes are occasionally present. The sputum may be scanty, and contain thick glairy mucous little balls in a clear, frothy mucus. These mucous balls are translucent to pale-grey or greyish-yellow in colour, rather resembling grains of boiled sago in appearance, and showing, microscopically, coiled-up cylindrical or sausage-shaped masses of thick mucous threads or definite Curschmann's or other spirals: and also the characteristic Charcot-Leyden crystals (*see* Fig. 411, p. 743). The sputum contains alveolar cells : catarrhal cells from the bronchi which often show increased oxyphil staining of their cytoplasm : and eosinophil leucocytes, sometimes in large numbers. The Curschmann's spirals occur in the sputum in practically every case of true bronchial asthma, and are found particularly at the end of the paroxysm. They consist of a mucous mantle, containing eosinophil and epithelial cells around a refractile central filament of altered mucus, often subdivided into fine fibrils. These spirals are found also in some cases of chronic bronchitis without symptoms of asthma. The asthmatic attack is regarded as an anaphylactic or atopic (p. 137) reaction, due to sensitisation of the patient to foreign proteins (pollen, hair, etc.) introduced into the body by inhalation or ingestion. An eosinophilia may be present in the blood in asthma and other forms of anaphylaxis. Thickening of, and hyaline change in, the basement-membrane of the medium-sized bronchi are constant microscopical features. The mucous glands of the bronchus become hypertrophied and their mouths widened so that they appear as diverticula of the bronchial lumen. The smooth muscle is also hypertrophied. Numerous eosinophils are found in the walls of the bronchi and in the peribronchial tissues.[1]

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[1] The following quotation from the Chevalier Jacksons' book, " The Larynx and Its Diseases," 1937, p. 416, is worthy of attention : " Finally, the diagnosis of *asthma* in any case should be only tentative until after bronchoscopy has demonstrated the absence of tracheal tumor. This rule applies whether the patient is allergic or not. All is not asthma that wheezes." To this we would ourselves add that the possible presence of *bronchial carcinoma* (pp. 569–576) should also be excluded.

Tumours of the Bronchi (p. 569).

SECTION III

DISEASES OF THE LUNGS

General Facts. Brief reference may be made to certain anatomical considerations which have an important bearing on the distribution and characters of pathological conditions in the lung.

The lung is composed of respiratory bronchi arranged in twelve segmental zones (p. 507), groups of lobular dilatations (air-sacs or infundibula) and pulmonary alveoli or air-cells—together with blood-vessels, lymphatics and nerves all bound together by connective tissue.

The extremities of the small bronchial tubes expand into passages from which a few blind sacs or alveoli open. These " respiratory " bronchioles have a long and tortuous course, with many branches (alveolar ducts), from the sides of which, throughout their course, blind polyhedral pouch-like bulgings (alveolar sacs and single alveoli) are given off. The openings from the alveolar ducts into the alveolar sac are called atria.[1]

The respiratory bronchioles are lined at their proximal parts with ciliated columnar epithelium like that of the small bronchioles from which they arise—but very soon the ciliated epithelium gives place to cubical or flattened, non-ciliated epithelium. Their walls are composed of connective tissue with bundles of smooth muscle and elastic fibres. The alveolar ducts are thin-walled tubes with the pouching already described, so that the wall is an interrupted one—that part between the pouches, *i.e.*, the mouths of the alveoli, contains smooth-muscle cells, and elastic and collagenous fibres. These alveolar sacs are closely packed together and, in their walls, there is a rich capillary network supported by a closely meshed reticulum of fine connective tissue with some elastic fibres. The generally accepted view is that the air-cells (alveolar sacs and alveoli) are lined by a " respiratory epithelium " (by many regarded as endothelium, *i.e.*, mesothelial in nature, reactions and origin—p. 358), composed of large, extremely thin squames in which nuclei are difficult to demonstrate, and that, in addition, groups of small cubical cells, peri-capillary in their distribution, are present, though inconspicuous. In regard to these squames there is, however, a growing tendency among histologists to deny their existence and to consider what appear to be " squames " mapped out by the silver-nitrate treatment as being in reality reticular fibres of the connective tissue of the alveolar walls, possibly also the outlines of endothelial cells of the capillaries and even of the peri-capillary cells. Rose, in a study of human embryos of different sizes, after distending the air-passages with fixing fluid, concludes that the future alveoli are at no stage lined by " epithelium," and that the alveolar sacs and alveoli are mesenchymal in origin, and Maximow and Bloom in their Textbook of Histology[2] (1938), p. 456, state that no epithelial structures have been proved to exist in the adult lung beyond the distal end of the respiratory bronchi.

In regard to the groups of cubical cells, these probably are remains of the " cuboidal epithelium " lining the alveoli in the embryonic lung. The free macrophages (alveolar phagocytes, "dust-cells," "heart-failure cells") have been commonly regarded as being derived from the " alveolar epithelium " or endothelium, but Maximow and Bloom, referring to the " cuboidal epithelium," state that, in tissue-cultures and in certain *in vivo* experiments, " these inconspicuous cells in the septa are seen to mobilise in a few hours and assume the appearance and function of typical macrophages. The name ' septal ' cells has been suggested for them." Some recent work, under the direction of one of our collaborators, supports the view that these phagocytic cells are derived from cells of a polyhedral shape and not from what has been usually described as the alveolar endothelium.

Besides the blood supplied by the pulmonary artery, there is, in addition, that supplied by means of the bronchial arteries. The bronchial arteries nourish the walls of the bronchi and the connective-tissue framework of the lung itself. The return-circulation for both the pulmonary and the bronchial arterial supply is carried on mainly through the pulmonary veins. The distribution of the lymphatics of the lungs is of considerable importance, for it is chiefly along these channels that irritant substances are carried to and from different parts of the organ. The lymphatics are found in the walls of the alveoli: also in the walls of the bronchi and the vessels: and another system commences immediately beneath the pleura, and penetrates along the various septa of the lung. The lymphatic trunks leave the lung at its root. Particles inhaled into the small bronchi and alveoli readily pass into the lymphatic system, and are carried along its channels by phagocytic cells and lodged in the fibrous-tissue framework of the lung itself, *e.g.*, in the subserous connective tissue, interlobular septa, peribronchial tissue, etc., and in the lymph-nodes and elsewhere.

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[1] The reader should refer for details to the illustrations in Schafer's " Essentials of Histology," 14th edit., 1938, edited by H. M. Carleton, pp. 318 *et passim.*

[2] *See* footnote on p. 30.

MALFORMATIONS :—Complete congenital absence or extreme smallness of one or both lungs has been described. Absence of one or more lobes is not uncommon. Other abnormalities, *e.g.*, in the size of the lobes, and the presence of additional sulci, are of frequent occurrence. Congenital abnormalities of the pulmonary vessels such as absence of one of the pulmonary arteries occasionally occur. For example, a bronchial, or even an intercostal, artery may arise directly from the aorta, enlarge and partially assume its functions.

INJURIES :—There seems little doubt that, in certain instances, clean perforating bullet-wounds of the chest may produce no serious pathological change. But, in the majority of cases, there is added to the simple puncture the effect of laceration (*e.g.*, from a fractured rib), contusion and hæmorrhage, and bacterial infection. The amount of destruction will, of course, depend on the shape, size, direction, and velocity of the penetrating missile, aided by the carriage into the wound of bits of clothing or other foreign bodies. The lung-wound in the majority of fatal cases is characterised by extensive damage, with hæmothorax and wide extravasation of blood into the tissues surrounding the track. Pneumothorax is not common in such cases. If the lung is healthy, hæmothorax generally causes collapse and hinders the spread of infection. Localised sepsis is common in these cases and may occur in both collapsed and uncollapsed lungs. The septic bronchopneumonia, starting from the wound and spreading throughout the lung, is always most evident in cases of laceration of the lung without hæmothorax. If hæmothorax occurs, the laceration itself is relatively harmless.

The effects of the bursting of high-explosive bombs and shells, or of the **exploding of balloons,** upon the chest and its contents, particularly the lungs,[1] may be serious, quite apart from the occurrence of superficial burns or direct injuries, penetrating wounds due to splinters, and contusion of the lung by concussion communicated through the chest-wall. The damage may take the form of acute distension of the lungs **from blast**, with, it may be, rupture of the visceral pleura and collapse of the lung : or acutely-produced traumatic emphysema (pp. 524–5 and 527) : and bilaterally-distributed hæmorrhages, including a varying amount of capillary hæmorrhage into the lung-tissues—sometimes with no external signs of injury. These hæmorrhages may fill the alveoli with fresh non-hæmolysed red corpuscles derived from the distended capillaries in the alveolar walls—the histological picture in some ways simulating the appearances seen in infarction of the lung. Injury from blast and from concussion, carbon-monoxide poisoning, and asphyxia from compression of the chest by earth, sand or debris, may each contribute to a fatal issue in these cases. If the patient survives the immediate effects of the explosion, the bleeding into the lungs may continue for some forty-eight hours, the scattered patches of hæmorrhage tending to spread and coalesce : and later becoming, perhaps, the seat of bronchopneumonia and collapse. Scattered amongst the red hæmorrhagic areas, there may also be ashen-grey friable patches with sharply defined margins ; and, in these, the alveoli are found to contain a fibrin-network, in the meshes of which are varying numbers of wandering cells (which may be predominantly monocytic) and partially hæmolysed red corpuscles. Hadfield,[1] from whose papers much of the above description is taken, notes the superficial resemblance of these patches to lobar pneumonia in the stage of red hepatisation.

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[1] "Experimental Study of Blast Injuries to the Lungs," by S. Zuckerman, Oxford, *Lancet*, 1940, ii, 219 : "Effects of High-Explosive Blast on the Lungs," by D. M. Dean and A. R. Thomas, R.N.V.R., *ibid.*, 224.

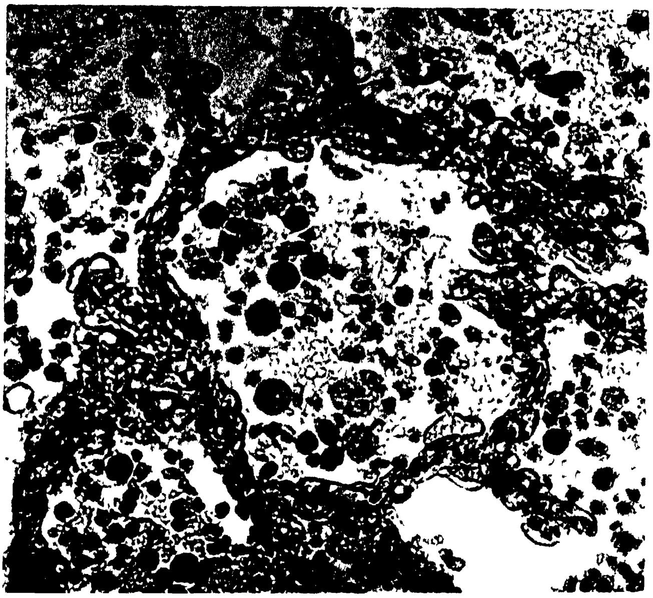

FIG. 302. *Lung in chronic venous congestion,* showing varicosity and thickening of the alveolar capillaries, and the presence of catarrhal cells and red corpuscles in the alveolar spaces. × 200.

GAS-POISONING :—The effects of heavy gases such as chlorine or bromine have been specially investigated, and chlorine was largely used as the drift-gas for offensive purposes during the war of 1914–18. As a result of its inhalation, great dyspnœa supervenes. There is intense congestion of the mucosa of the trachea and larger bronchi ; the tubes become filled with a thin, pale-yellow, frothy secretion, which is highly albuminous. The lungs show severe œdema and congestion, with irregular areas of emphysema—apparently produced acutely. Convalescence is slow and prolonged, with the occurrence of chronic bronchitis.

With "phosgene-gas" (carbonyl chloride) the occurrence of serious symptoms may be delayed for several hours, but the results, in the lungs and air-passages, are very similar to those obtained with chlorine, though it is not uncommon to find capillary thrombosis in the lungs. The pathology of the effects of "mustard-gas" (dichlordiethyl sulphide) is different. After a period of twenty-four hours, an intense inflammatory reaction is set up which ends in the complete necrosis of the bronchial mucous membrane. At a later period, in those who survive, fibrosis occurs around the bronchi ; and a liability to bronchitic attacks ensues. There seems little doubt that the various forms of gas-poisoning may stimulate latent tuberculosis into activity, but pulmonary tuberculosis *de novo* is not a common sequel.

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[1] "Blast from High Explosives," by Geoffrey Hadfield *et al.*, E.M.S., *Lancet*, 1940, ii, 478 : and *Brit. Med. Jour.*, 1941, i, 77.

DISTURBANCES OF THE CIRCULATION :—

(*a*) **Active Hyperæmia (Acute Congestion)** (p. 527).

(*b*) **Passive Hyperæmia or Venous Engorgement.** Venous engorgement may occur rapidly, especially in conditions which lead to sudden heart-failure just before death, in cerebral lesions, *e.g.*, epilepsy, coma, etc., and also in cases where thrombosis of the pulmonary veins has occurred ; but it is more often a slowly-developed and chronic affection, and is described under the term **Chronic Venous Congestion** (pp. 150–1). It is due to any cause which prevents the free return of blood from the lungs, such as stenosis or incompetence of the mitral valve, or muscular weakness due to degenerative changes and loss of driving power of the heart. Even when, by hypertrophy of the various chambers of the heart, and especially of the right ventricle (p. 460, Fig. 260), circulatory compensation seems to be established, there is still an increase of pressure in the pulmonary circulation, and, in consequence, venous engorgement. If compensation is not fully established, the engorgement becomes more pronounced; and ill-defined, indurated patches, varying considerably in size, and often situated towards the lower part of the lung, are produced. They are most abundant where there has been much capillary hæmorrhage. The lung, especially at these areas, is of a dark brick-red colour, and is tough and firm—the condition known as **brown induration.** On **microscopical examination,** the veins and capillaries are seen to be distended, those in the alveolar septa being prominent, giving to the latter a beaded appearance (Fig. 302, p. 519). The walls of the distended vessels are thickened, and many of the alveolar spaces contain blood and catarrhal cells, in some areas so abundant that the lung is rendered almost airless. The catarrhal cells or " heart-failure " or " heart-lesion " cells (Fig. 70, p. 150) originate mainly as desquamated endothelial cells of the alveoli. Those derived from the septal cells are phagocytic, take up red corpuscles and pigment, and also any particles of carbon which may be present, pass into the lymphatics of the alveolar walls, and are carried to the peribronchial and perivascular lymphatics, to the lymphatics in the deep layer of the pleura, and to the bronchial lymph-nodes—in all of which situations they deposit their pigment. In addition to the thickening of the walls of the veins and capillaries, there is also an increase of fibrous tissue throughout the lung. In this thickened fibrous tissue, and also in the alveoli, the pigment, derived from the blood, is present in the form of brown granules. It is probable that this pigment, by the irritation of its presence, is responsible for at all events a proportion of the fibrous overgrowth.

The vessels in the bronchial wall, and especially those of the smaller bronchi, where there is an anastomosis between the pulmonary and bronchial circulations, become distended. In addition, there is thickening of both the mucous and submucous coats of the bronchi, leading to catarrhal changes and even to obstruction. Hæmorrhage may occur from rupture of the over-distended vessels in the bronchial walls or in the lung-alveoli.

The **sputum**, especially in cases due to mitral disease, consists of white mucus with areas of "rusty" colour, or of a uniformly rusty mucus. The colour is due in part to blood, but mainly to phagocytic cells loaded with golden-yellow granular pigment derived from the red corpuscles (Figs. 69 and 70, p. 150).

(*c*) **Pulmonary Embolism and Thrombosis.** Pulmonary emboli originate from vegetations on the right side of the heart, thrombi in the right auricle (atrium) or ventricle, or thrombi in the systemic veins : and, during or after childbirth, not only from the breaking-down of thrombi in placental or uterine and adjacent veins, but from the passage of fœtal products (epithelial squames and other debris of the vernix caseosa, liquor amnii and meconium) into the maternal circulation, with the impaction of the more solid particles in the smallest branches of the pulmonary arteries, arterioles and capillaries, and perhaps death with symptoms resembling those of anaphylactic shock. These emboli do not necessarily produce infarction. If they are septic, softening of the walls of the vessel may take place and aneurysms be formed. This condition of embolic aneurysm in the lung is rare (Fig. 288, p. 496). Emboli giving rise to pyæmic abscesses are described on pp. 167 to 170 and 500–1. The subject of embolism and thrombosis in the lung is discussed on pp. 176–8.

(*d*) **Pulmonary Infarction** is frequently associated with chronic venous congestion. The raised, dark plum-coloured areas stand out prominently on the surface of the lung. This subject is dealt with under Circulatory Disturbances (pp. 176–178).

ŒDEMA OF THE LUNGS occurs in nephritis with general œdema and in patients with cardiac weakness or myocardial disease, especially of the left ventricle. The œdema seen in anæmia and in other debilitating diseases is due in part to the weakened action of the heart. In nephritis, œdema occasionally develops very rapidly, and may be confined to one lung, or even to a single, *e.g.*, the upper, lobe. The bases of the lungs, however, are generally most affected, gravitation being an important determining factor. If the patient is not bedridden, the lower lobes especially are involved ; and, if he is lying on his back in bed, it is in the posterior parts that the most intense degree of œdema is found. This œdema is partly inflammatory in nature, resulting from the exudation of lymph from the distended vessels. Where congestion is considerable, and especially where the œdema is present only at the basal parts of the lower lobes, the term **hypostatic engorgement** or **hypostatic congestion** is applied to the condition (p. 160). The affected parts assume a dark blue or purplish-red colour, and are more solid than normal. If the lung is incised and squeezed, a frothy fluid, mixed with blood or blood-pigment, can be expressed from the cut surface. On **microscopical examination,** the capillaries are distended, and the alveoli contain some fine amorphous granular material (Fig. 306, p. 529)—indicating the presence of serous fluid—and perhaps a few red corpuscles. Catarrhal cells, in larger or smaller numbers, may also be present.

The **sputum** is frothy, colourless or blood-stained, and watery.

In œdema (p. 178) without venous congestion, the lungs are pale, and a clear, pale yellow, frothy liquid can be expressed in considerable quantities from the cut surface. This condition is often pronounced in cases of Addisonian anæmia (p. 653).

ATELECTASIS AND COLLAPSE :—

The term "atelectasis" [1] has been applied to two distinct conditions—correctly to one, in which the lungs have *never been expanded* with air—incorrectly in the case of the other, in which the previously-expanded lung has become compressed or collapsed. The latter should be called "collapse."

Congenital Atelectasis—or **Atelectasis proper**—is found in new-born infants where the inspiratory power has been insufficient to expand the lungs, and is, of course, **complete** where death of the fœtus has occurred *in utero*. Deficiency of inspiratory force may result from general weakness, from compression of the thorax, or from interference with the respiratory centres by cerebral hæmorrhage or by drugs administered to the mother ; or it may be produced by obstruction of the air-passages by foreign material, *e.g.*, meconium or mucus.

When atelectasis is **partial**, its commonest situation is in the lower lobe, especially the posterior part, though it may be more widely spread and be seen in the middle lobe of the right lung, the edge of the left lung where it overlaps the heart, or even involving the whole of one lobe. The unexpanded area is dark-reddish in colour, tough in consistence, airless, and depressed below the level of the surrounding lung-tissue. In its general naked-eye appearance, it cannot be distinguished from true collapse ; but, on **microscopical examination,** the absence of catarrhal cells and inflammatory exudate from the unexpanded lung indicates that the child was still-born or died soon after birth. In such cases, the area involved can be inflated from the communicating bronchi. If the child survives, proliferative changes take place in the connective tissue, the septa between adjacent alveoli may become united to one another, and obliteration of the alveoli may result. Some cicatrices seen in the adult lung are supposed to result from the atrophy of these unexpanded areas. Secondary dilatation of the bronchi and bronchioles occurs in consequence of atelectasis, and, by some authors, is regarded as compensatory.

Collapse. Collapse of the lung after it has become expanded may take place in young infants, and cannot, without microscopical examination, be distinguished from congenital non-expansion or atelectasis ; but the variety of collapse to which reference is now made here is that which occurs later in life. It may involve practically the whole of the lung, or it may be partial in its distribution.

(*a*) **Collapse of practically the entire lung** may result from compression from without by pleural effusions or by large tumours. The lung is pressed backwards and inwards towards its root. It becomes of a slaty-grey colour, and is tough and fleshy in consistence. If the collapse persists for a long period, atrophy of the aerating tissue of the lung takes place, accompanied by dilatation of some of the larger bronchi, and by a fibrous overgrowth of the connective tissue in the deep layer of the pleura, the interlobular septa, and the perivascular and peribronchial sheaths. The blood-vessels become thrombosed and in varying degree obliterated by endarteritis. The portion of lung immediately adjacent to the root often escapes, even in extensive collapse.

(*b*) **Collapse of portions of the lungs** is brought about by any causes which diminish the inspiratory force or obstruct the entrance of air into the lungs. Such factors are aided by conditions which mechanically compress the lung and force out the air, such as effusions of liquid or air into the pleural cavity.

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[1] "Atelectasis," from Greek, ἀ-τελής, *a-telēs*, without end, hence incomplete : and ἔκτἄσις *ektasis*, extension or expansion, from ἐκτείνω, *ekteinō*, I stretch out to the full.

Weakening of the thoracic wall, *e.g.*, in rickets, deformities of the chest as in scoliosis, weakening of the thoracic muscles in certain forms of paralysis, or even in cases of general debility, act by diminishing the inspiratory force ; whilst distension of the abdominal cavity with fluid or tumours, dilatation of stomach or intestine, enlargement of the heart or effusions into the pericardial sac, tumours in the thorax, or even the recumbent position of a weakened patient, will act by impeding the full expansion of the lungs and aid in the production of collapse.

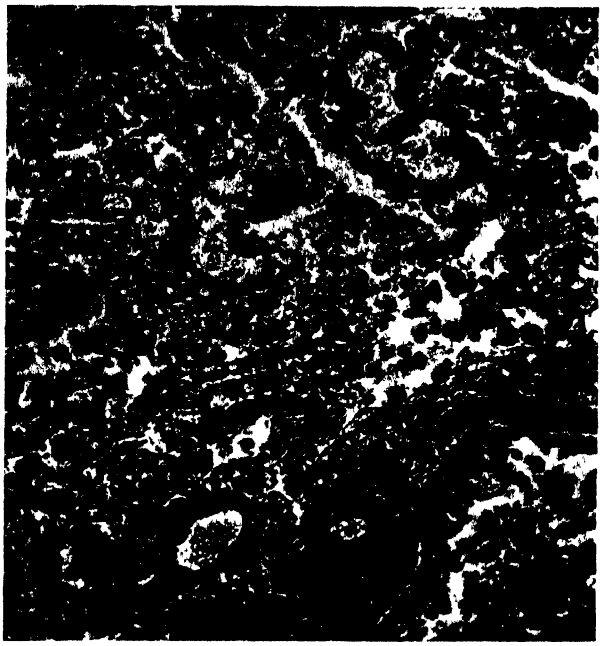

FIG. 303. *Collapse of lung.* Note the folding together and compression of the air-spaces, and the beaded appearance of the capillaries in their walls. A section of part of a bronchus, blocked by inflammatory exudate, is seen at the lower right-hand corner of the figure. × 200.

Obstruction to the entrance of air into the lungs is caused by pressure on the bronchi by aneurysms or tumours : the lumen may be blocked by a bronchial carcinoma growing from the mucous membrane : or by the presence of a membranous exudate in the larger bronchi, as in diphtheria, or the presence of foreign bodies, blood, or bronchial secretion in the smaller divisions of the bronchial tree.

The commonest sites of **partial collapse** are the lower and posterior parts of the lungs, the free edges at the base, the middle lobe of the right lung, and the edge of the left lung where it overlaps the heart.

A **lobar collapse** or the collapse of the greater portion of a lobe, especially of the lower lobe of the right lung (" massive collapse "), is sometimes seen one or two days after abdominal operations. The chest-wall is retracted and the heart displaced to the affected side. The condition usually passes off rapidly.

The mechanism of its production is not clear, but it is suggested that the causal factors are bronchial obstruction by muco-purulent exudate and a relative immobility of the diaphragm produced by distension of the abdomen from causes such as enlargement of the spleen or liver or gaseous distension of the stomach or intestines.

Morbid Anatomy. The collapsed areas are irregular in shape, but well defined in outline. When occurring at the surface of the lung they are of a dark slaty-blue or purple colour, are depressed below the general surface, and their margins correspond to interlobar septa. If the condition is uncomplicated, the pleura over the collapsed patches is glistening, and shows no evidence of acute inflammation. On section, the collapsed portions of the lung are smooth and firm, dark brownish-red in colour, and often almost airless and bloodless, and may sink in water. Because of the collapse of the intervening air-tissue, the bronchi and blood-vessels are huddled together, and thus *appear* more numerous than normal. **On microscopical examination,** the walls of the air-spaces are folded and compressed, and may be in contact with one another, their cavities completely, or almost completely, obliterated (Fig. 303). Chronic venous congestion and catarrhal changes are associated with the collapse, and some of the air-spaces, lined by polyhedral or rounded cells similar to those present in the fœtus, may be seen in a partially collapsed state. Fibrosis accompanied by bronchiectasis may occur, particularly when the cause of the collapse has been an inflammatory exudate in the pleural cavity and where the fibrinous exudate on the pleural surface has become organised and the lung enclosed in a fibrous envelope.

Lobular collapse is commonly associated with capillary bronchitis (p. 533), especially in children, and is rapidly followed by acute congestion, and, later, by lobular pneumonia. Very frequently, around these areas of lobular collapse, there is a zone of lobular emphysema. On naked-eye examination, a roughly polyhedral depressed area, corresponding to the collapsed lobule or group of lobules, is seen.

EMPHYSEMA :—

In this condition of " over-inflation of the lung," either the air-vesicles or the potential tissue-spaces of the interstitial fibrous-tissue framework of the lung are distended with air. Hence two main varieties of emphysema are described —(1) **vesicular,** in which the air is contained within the abnormally-dilated air-vesicles : and (2) **interstitial,** in which, as implied by the name, the interstitial tissue of the lung is its site.

Vesicular Emphysema. If obstruction of a bronchus is partial or intermittent, the inspiratory and expiratory efforts may not be balanced, and the obstruction, acting as a valve, may allow of entrance but prevent free exit of air, with resulting over-distension of the lung-alveoli. The **acute** forms of emphysema, which occur around areas of collapse in capillary bronchitis (see above and p. 533) and in bronchopneumonia, may be explained in this way—the obstruction being due to the swelling of the bronchial mucous membrane or the retained tough bronchial secretion. In **asthma,** emphysema is also present, and, though plugs of mucus may be found in the bronchi, the main obstructive factor is the spasmodic contraction of the bronchial muscle. **Acute traumatic emphysema** may be caused by the blast of explosives (pp. 518 and 527). In addition to these acute forms of vesicular emphysema, there is a **chronic** type which is divided into two varieties. In one the lungs are small, and in the other they are voluminous.

The former—**Atrophic emphysema**—is associated with, and caused by, the impairment of nutrition, and the degenerative changes in the elastic tissue of the lungs in old age, Addisonian anæmia, chronic wasting diseases and chronic lead-poisoning. There is not necessarily any element of increased intrapulmonary pressure in its causation, though this may be, and often is, present.

The **large-lunged emphysema** is the commoner type, and is caused mainly by repeated over-distension of the alveoli by the constantly recurring cough associated with diseases such as chronic bronchitis and spasmodic asthma. As a result of the permanent over-distension, the elastic tissue degenerates, there is interference with the blood-supply, the alveolar septa break down and adjacent alveoli come to communicate with one another.

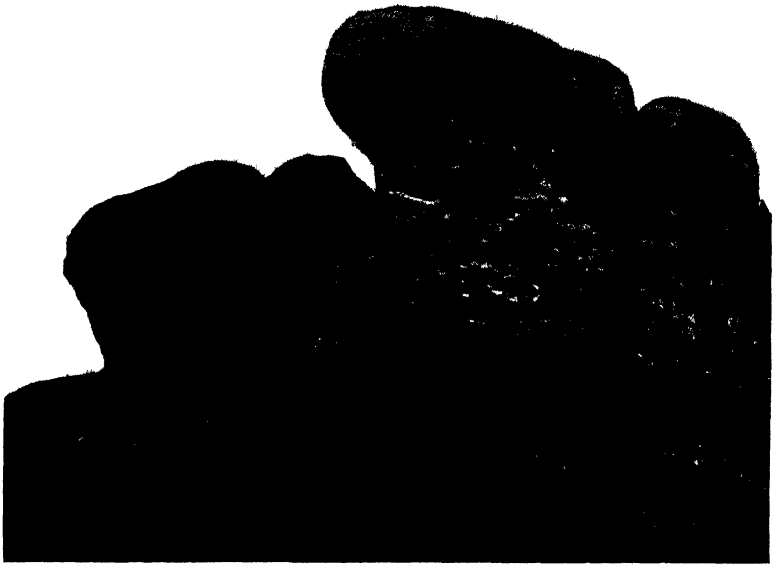

FIG. 304. *Large localised emphysematous bullæ at apex of left lung,* due to secondary infiltration with bronchial carcinoma (the whitish tissue below the larger bullæ) (W. E. H. case) (half natural size).

Many authorities hold that the distension is caused by forced expiratory efforts with the glottis closed, but it seems reasonable to regard the forced inspiration which follows the coughing or which occurs during the spasmodic attacks in asthma as an equally, if not even more, important factor in the causal mechanism. Obstruction to the entrance of air into one part of the lung leads to an increase in the inspiratory expanding force in the neighbouring parts, with consequent distension of the air-spaces and the production of complementary emphysema. This inspiratory form occurs especially round collapsed or consolidated areas of lung-tissue. It is well illustrated in cases of lobular collapse, in bronchopneumonia, and also in asthma.

In the localised emphysema seen round areas of airless lung-tissue such as fibroid nodules or in the neighbourhood of tumours, very large bullæ may be produced (Fig. 304).

Distribution of the Change. The commonest situations in the lung in which emphysema occurs are those in which its tissues are least supported, for example, the anterior margins (especially on the left side, where the lung overlaps the pericardium), the anterior and posterior aspects of the lower margins, the right middle lobe, and the apices.

Morbid Anatomy. In the atrophic type, the lungs are small and usually do not overlap the pericardium. They may weigh only 8 or 9 ozs. as compared with 20 to 30 ozs. for the normal lung. In the "large-lunged" type, the lungs are voluminous, their anterior margins meeting at, or even crossing, the middle line, and also overlapping the heart to an abnormal degree, in some instances completely covering the "bare area" of the pericardium. At parts, large, irregular, thin-walled, bullous projections may be seen. In both types, the lungs are extremely light, pale in colour and almost bloodless—the interlobular septa being often mapped out by the presence of carbon-pigment. On section, the tissue is dry, soft, and spongy, or like a "down-quilt" in consistence, and the air can be moved readily from one group of air-spaces to another. The air-cavities are dilated and their walls stretched and thinned. Partly on account of the stretching, and partly owing to interference with their vascular supply, the intervesicular septa undergo atrophy and give way, and intercommunication takes place between the adjacent air-spaces (Fig. 305). The stretching, due to increased internal air-pressure, plays practically no part in the production of the atrophic type, the atrophy being due almost wholly to malnutrition. The interlobular septa are often thickened. The smaller branches of the pulmonary arteries may exhibit fibrosis, and the larger branches atheroma. In the large-lunged type of the disease, the obstruction to the pulmonary circulation, due largely to the obliteration of alveolar capillaries, causes dilatation and hypertrophy of the right ventricle

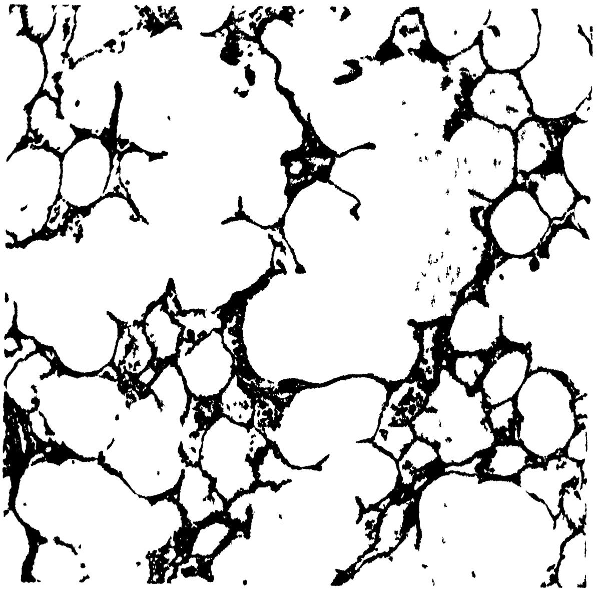

FIG. 305. *Emphysema of lung*, showing distension of the air-vesicles, with thinning, atrophy and breaking-down of the interalveolar septa. × 50.

and dilatation of the pulmonary artery ; whilst, in the atrophic form, if not associated with chronic bronchitis, cardiac hypertrophy does not take place.

Interstitial Emphysema. In this somewhat rare condition, the air is found, either in the interstitial tissue of the lung alone, or it may, in addition, be widespread in the cellular tissues of the mediastinum, neck, chest-wall, or even over almost the whole body. This form of emphysema may occur from rupture of the lung-tissue during an attack of whooping-cough, or as a result of great exertion, *e.g.*, in the course of difficult labour. Sometimes, it results from the rupture of an emphysematous bulla, or from a wound of the lung, trachea, or bronchi, or from injury to the lungs from the effects of the blast of explosives (pp. 518 and 524–5). Thus, in laceration of the lung by a fractured rib, a varying degree of interstitial emphysema generally results. The condition may spread along the root of the lung to the cellular tissue of the mediastinum, root of the neck, etc.

Interstitial emphysema may be simulated *post mortem* by the presence of bubbles of gas produced in the tissues of the lungs as a result of decomposition.

INFLAMMATION OF THE LUNG

(*a*) **ACUTE CONGESTION** or **ACTIVE HYPERÆMIA** results from the action of bacterial and toxic irritants, and may be merely part of a general infection. In lobar pneumonia, there is a preliminary stage of acute congestion, and this congestion may occur also in other toxic and septicæmic conditions, as, for example, in the acute infective fevers, without necessarily being followed, as in the case of pneumonia, by consolidation. It is characterised by dilatation and engorgement of the alveolar capillaries (Fig. 306), the walls of which, however, are not thickened, as they are in chronic venous congestion. The alveolar spaces may be empty, or may contain, in varying proportions, blood, transuded lymph, or fibrin derived from these, and perhaps inflammatory cells.

(*b*) **ACUTE LOBAR PNEUMONIA (CROUPOUS** or **FIBRINOUS PNEUMONIA)** is an acute infective disease the pyrexial period of which lasts some six or seven days, the fever terminating by crisis (p. 141 and Fig. 62, p. 142), though in some cases the fall in temperature is gradual. Some authors regard the disease as a septicæmia, in which the special local lesion is in the lung. Though it is true that invasion of the lung is only one of many possible local manifestations of pneumococcal infection : that pneumococci may produce septicæmia without any true pneumonia : and that, in cases of pneumonia, the organism is found, by cultural methods, to be present in varying numbers in the blood-stream : yet the localisation of the disease is so frequently in the lung that most authors agree in regarding it as the principal seat of infection.

Ætiology. The chief causal organism is the *Streptococcus pneumoniæ* (*Pneumococcus* of Fränkel). It is found in enormous numbers in the sputum and in the lungs, and is also, as explained above, present in the circulating blood. In a certain proportion (less than 5 per cent.) of cases, *Klebsiella pneumoniæ* (*Pneumobacillus* of Friedländer) appears to be the cause. Staphylococci and streptococci are capable of causing a somewhat similar condition, especially in association with other bacteria such as Pfeiffer's bacillus or the bacillus of bubonic plague. The consolidation in these cases occurs usually as irregular patches, which may coalesce and produce an appearance simulating acute lobar pneumonia. In the great majority of cases of typical acute lobar pneumonia, the causal pneumococci have been differentiated by serological tests into three main types, types I and II being responsible for most of the cases. Type III is the *Pneumococcus mucosus* and is the cause of a severe and fatal form of the disease. In addition to these three types, another group, group IV, which contains a number of serologically distinct strains, is responsible for pneumonia of a relatively mild character. From the original type IV group, at least thirty different strains have been isolated and given a numerical designation. For the selection of the appropriate therapeutic antibacterial serum (if employed in addition to chemotherapy with some member of the sulphanilamide group), it is essential that the **type** of the infecting organism be known in each instance. Methods of sputum-typing are utilised for this purpose.

Though, as has been stated above, the commonest strains, at all events in adult patients, are types I and II, the relative proportion of these varies in different localities and in the same locality at different periods of the year. According to Blacklock, 90 per cent. of the cases of bronchopneumonia in children, which have come under his observation in Glasgow, are due to pneumococci belonging to group IV, strains of which are often present in the nasopharynx of both children and adults in normal health. Though the pathological changes, the mortality, and the infective nature of the disease are dependent largely upon the type of organism concerned, yet the degree of susceptibility of the patient is also an important factor in determining the site and severity of the infection.

Certain predisposing causes, such as exposure to cold, fatigue, etc., have long been recognised by clinicians as aiding in the production of pneumonia. These cannot be overlooked, and must be regarded as predisposing factors.

Experimental Pneumonia. Blake and Cecil (1920), Gaskell (1925), and other workers have demonstrated that lobar pneumonia can be produced in monkeys and in rabbits by introducing into the trachea, or directly into the lung-tissue, special strains of pneumococci. Though there may be acute inflammation in the terminal bronchi and alveoli in such experimental infection, an early manifestation is an acute lesion in the interstitial tissue at the root of the lung, and a peripheral extension to the alveoli by way of the perivascular and peribronchial lymphatics. The alveoli seem to be involved mainly by the passage of the infective material through their walls. In these experiments, pneumonia was not produced when the organisms were introduced into the subcutaneous tissues or into the blood, or were sprayed into the nose or naso-pharynx.

Site of Origin and Mode of Spread. From these experiments, it seems that, at all events in the species of animals employed, the infection takes place only when certain strains of pneumococci reach the smaller bronchi, as may occur naturally when small droplets of infected material such as sputum are deeply inhaled and come to rest in these bronchi near the root of the lung. The infection then spreads through the walls to the alveoli. In man, acute lobar pneumonia, originating near the root of the lung, spreads, with a sharply defined margin, outwards and downwards in the lower lobe, or on the right side directly outwards to the middle lobe. There is a tendency for the disease to involve the whole or the greater part of one lobe, hence the term " lobar " pneumonia ; or it may spread more widely and involve the upper lobe, or almost the whole lung.

It is rare to find two separate areas in the same lung affected, but both lungs may be involved, the latter condition being known as "double pneumonia."

Pathological Anatomy. Typical cases of lobar pneumonia pass through several distinct stages.

(i) **The Stage of Acute Congestion.** Reference has already been made to this (p. 527). The affected area shows the ordinary phenomena of the early stages of acute inflammation, *i.e.*, distension of capillaries and venules, and exudation of lymph which passes into the alveoli and produces a condition of inflammatory œdema (Fig. 306). The cells lining the alveoli show swelling, or even proliferative changes, and a few leucocytes have migrated from the distended vessels. Hæmorrhage into the alveoli may also occur during this stage.

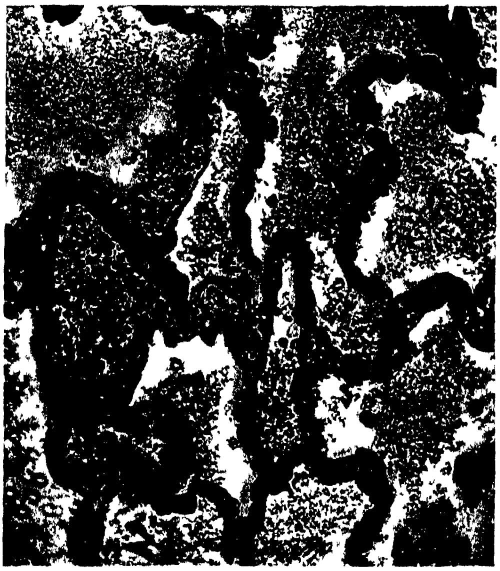

Fig. 306. *Acute congestion of lung,* showing dilatation of vessels in the alveolar walls and œdema in air-spaces. × 200.

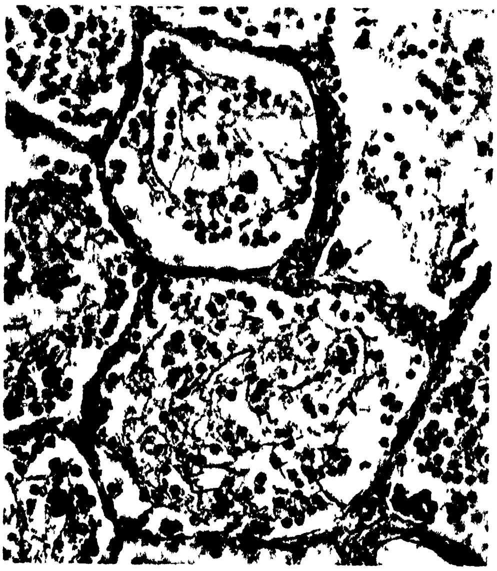

Fig. 307. *Acute lobar pneumonia in the stage of red hepatisation.* The air-spaces contain a loose exudate of fibrin and leucocytes, mainly polymorphs. × 200.

(ii) **The Stage of Red Hepatisation.** This is merely a further stage of the acute inflammatory process. The distension of the vessels is more evident, the exudation of lymph persists, and, in addition, the emigration of the leucocytes has become pronounced. The air is displaced, and the lung becomes consolidated and expanded—the consolidated lobe being considerably increased in bulk. The cells lining the air-spaces undergo proliferation, and some are found in the exudate as mononucleated phagocytic cells.

Naked-eye Appearance. The affected lung, or part of it, is airless and solid, and, if the inflammation reaches the serous surface, there may be an associated acute pleurisy, showing either as a slightly granular-looking, sticky exudate or, more typically, as a thick, yellowish-white, soft and friable fibrino-purulent layer, which can be easily stripped from the surface. On section, the consolidated area has a bright-reddish or reddish-grey, granite-like appearance, is friable, more or less smooth and uniform, and stands above the general level of the non-consolidated tissue. The consolidation in lobar pneumonia produces an appearance resembling that of a solid organ such as the liver, hence the term "hepatisation" applied to it.

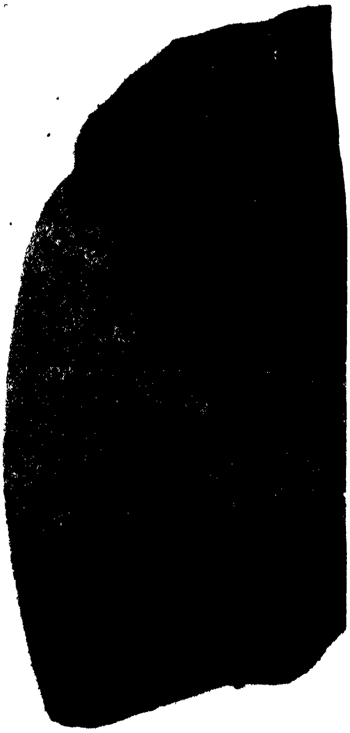

FIG. 308. *Lung*. Acute pneumonia. The lower lobe is completely consolidated in the stage of grey hepatisation and the lower half of the upper lobe is also solid—but in a somewhat earlier stage (red to grey hepatisation).

On microscopical examination, the appearances vary considerably. The air-cells are filled with fibrin, leucocytes, mainly of the polymorphonuclear variety, red corpuscles, and mononucleated phagocytic cells, in varying proportions; and the walls of the alveoli are congested. The causal organisms may be found in enormous numbers in the exudate. The fibrous septa of the lung are swollen and infiltrated with leucocytes; there is always an associated acute bronchitis; the bronchial lymph-nodes are swollen, soft, congested, and sometimes œdematous, and the process may spread to the mediastinal connective tissue as a mediastinitis. The microscopical changes in the pleura are described under Diseases of the Pleura, p. 579. (*See also* under Inflammation, Chapter II, p. 22.)

Results. The lesion may now, in favourable circumstances, pass to the stage of resolution, described below, or, under less favourable conditions, to the stage of grey hepatisation.

(iii) **The Stage of Grey Hepatisation.** In this stage, the lung remains solid, the congestion begins to pass off, and the cellular exudate tends to undergo degenerative changes. Thus, the lung is paler in colour, somewhat resembling grey granite, and, on section, appears finely granular. The tissue is very friable, and, on squeezing the lung, a sticky semi-purulent fluid containing fine granules of fibrin from the alveoli may exude from the cut surface or can be scraped off with a knife. **On microscopical examination,** the contents of the air-spaces are seen to be retracted from the walls (Fig. 309), the cells and fibrin are still present, the polymorphonuclear cells are in greater numbers, and many of them exhibit karyolysis, karyorrhexis, and other degenerative changes. The mononucleated phagocytic cells, especially in the less severe cases, are increased in numbers at this stage. The congestion of the vessels in the inter-alveolar walls is diminished, and may have completely passed off. Bronchitis is commonly seen in the smaller bronchi, and the exudate on the pleural surface may have become partially organised.

(iv) **Further changes which may occur in the consolidated lung:**—

I. If the disease has been arrested, absorption of the inflammatory products follows. This stage of **resolution** may supervene upon those of acute

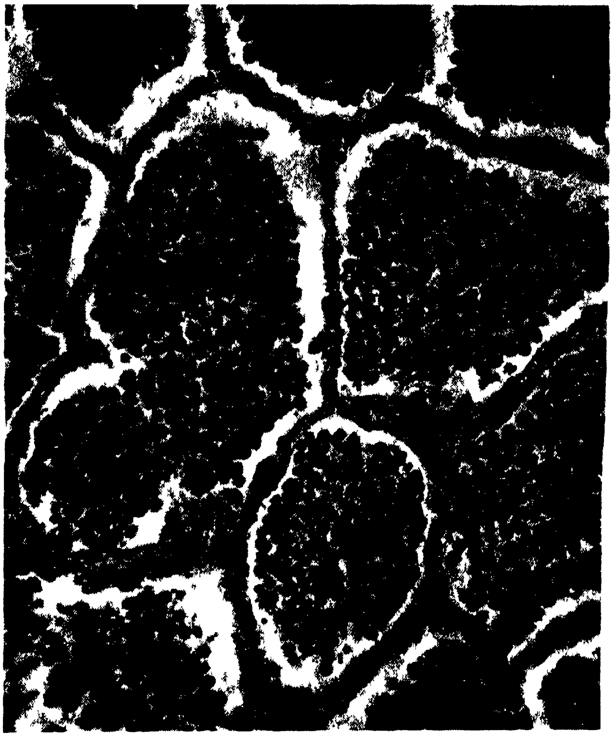

FIG. 309. *Lung* Acute pneumonia in the stage of grey hepatisation Note the excess of cells over fibrin in the alveoli, the retraction of the exudate from the alveolar walls, and the comparative absence of congestion in the latter × 230.

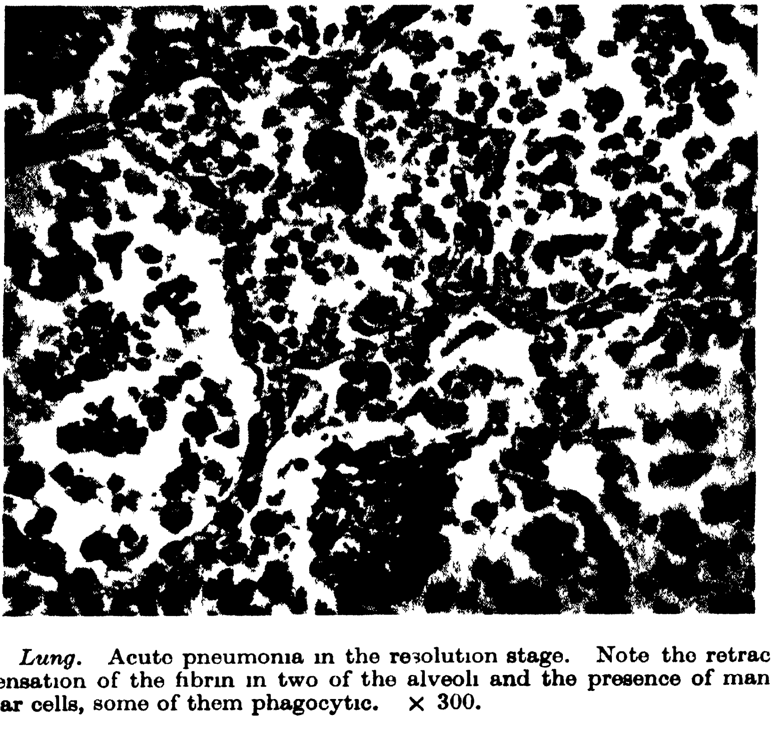

FIG 310. *Lung*. Acute pneumonia in the resolution stage. Note the retraction and condensation of the fibrin in two of the alveoli and the presence of many mono nuclear cells, some of them phagocytic. × 300.

congestion or red hepatisation, but it takes place much more rarely, or less effectively, if grey hepatisation has occurred, and probably not at all if the grey hepatisation is pronounced. During the process of resolution, the fibrin and other contents of the air-spaces become retracted and may partly be expectorated, and partly undergo gradual liquefaction and absorption. In some cases, especially in children, resolution is carried out almost wholly by the process of absorption, little or none of the exudate being expectorated as sputum. The cells lining the alveoli and bronchioles proliferate and bring about repair of the damaged portions. Eventually, the lung may be completely restored to its normal condition.

II. In less favourable circumstances, the resolution may be incomplete, or complications of various kinds may arise. Thus :—

1. Areas of softening and of suppuration may appear, giving rise to localised **abscess-formation** ; or a more **diffuse suppurative infiltration** of the pneumonic area may supervene. This is not common, but may occur especially in diabetes mellitus and in chronic alcoholism.

2. **Gangrene of the lung** may result from the additional action of organisms causing putrefactive changes, and this serious result, as in the foregoing diffuse suppurative lesion, is found not infrequently as a consequence of the lessened resistance of patients suffering from diabetes mellitus or chronic alcoholism.

3. **Chronic interstitial pneumonia** may be a sequel of imperfect resolution ; and, associated with the resulting overgrowth of fibrous tissue, atrophy of the aerating tissue of the lung occurs. The contraction of the newly-formed tissue may exercise external traction upon the bronchi and lead to their dilatation—bronchiectasis (p. 512). In certain rare instances, organisation of the intra-alveolar exudate may occur, capillaries and fibroblasts passing in from the walls, a process known as **carnification.**

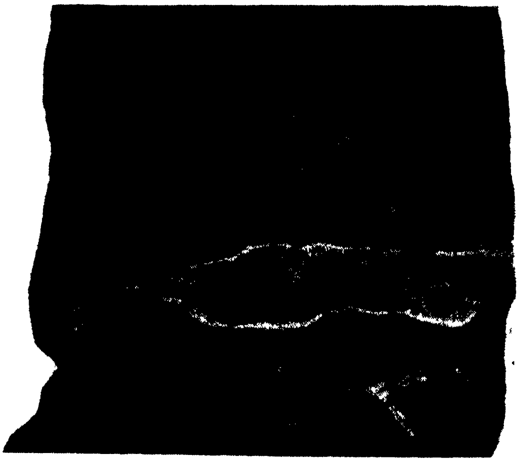

FIG. 311. *Lung.* Interlobar empyema in acute lobar pneumonia. Note the fibrinopurulent exudate between the lobes, forming a cavity which contained pus. (By courtesy of Dr. Norah Schuster.)

4. Rarely is there any considerable amount of serous fluid in the pleural cavity, but the fibrinous exudate may soften and become purulent, giving rise to **empyema** (p. 580). Such an empyema may be general, or localised by adhesions,

e.g., between the lobes (Fig. 311), or on the diaphragmatic, or on the outer, surface. As resolution proceeds, the pleural exudate undergoes organisation, (*q.v.* Repair, p. 49), and thus adhesions are formed between the visceral and the parietal pleura, and between the adjacent lobes. These adhesions may be extensive, and in some cases the whole pleural cavity may become obliterated.

5. Pneumonia being an acute infective septicæmic disease, the pneumococci are liable to become lodged in situations other than the lung, and thus cause complications such as pericarditis, endocarditis, meningitis, peritonitis and arthritis. **Pericarditis** may develop also by direct spread from the portion of the lung which overlaps the heart, and a certain degree of **mediastinitis** is common.

The toxins act on the various organs, producing the changes—for example, cloudy swelling, and fatty degeneration—generally seen in acute febrile diseases. A considerable neutrophil leucocytosis occurs as a result of a leucoblastic reaction in the bone-marrow (pp. 614 and 619). In some cases, especially in chronic alcoholic patients (p. 621), and in agranulocytosis (p. 636–7), this leucocytic reaction is feeble or absent. Its absence or its disappearance before the crisis means a want of response in the bone-marrow and is of grave prognostic significance.

The **sputum** in acute pneumonia is mucoid and abundant, and, early in the disease, is blood-stained. Later, it becomes rusty-looking and very tenacious, and, in this stage, is characteristic. The colour is due to altered hæmoglobin. If there is much catarrh of the larger bronchi, mucopurulent masses are present in varying quantity. Frequently, streaks of blood are seen, and at times the sputum consists of almost pure blood. Branching fibrinous casts are sometimes found. Microscopically, various cells are present—polymorphonuclear leucocytes, epithelial and endothelial cells, lymphocytes, etc. At the crisis, the sputum loses its rusty colour and becomes mucopurulent, and, later, consists mainly of mucus.

A greenish sputum, in the absence of jaundice, is often an indication of suppurative changes or of tuberculous infection. Where necrosis or gangrene follows on pneumonia, the sputum becomes more fluid and assumes a prune-juice or chocolate-brown colour, and the odour is fœtid.

(*c*) **ACUTE NON-SUPPURATIVE BRONCHOPNEUMONIA (CATARRHAL** or **LOBULAR PNEUMONIA).** This condition practically always begins as an inflammation in the smaller intralobular branches of the bronchi—**capillary bronchitis.** The walls of these become congested, and this congestion spreads to the walls of the neighbouring air-cavities, into which hæmorrhage and some fibrinous exudation occur. The affected bronchus or bronchiole becomes blocked with exudate and secretion, and, as a result, the portion of lung-tissue supplied by that bronchus or bronchiole undergoes collapse. The inflammatory process spreads, not only to the adjoining air-vesicles through the thin walls of the bronchus, but also along its interior to the collapsed area, which becomes the site of congestion, leucocyte-accumulation, fibrin-exudation, etc. In this manner, irregular consolidated patches of bronchopneumonia are formed. Some of the neighbouring air-cavities, receiving more than their due share of the inspiratory distending force, become emphysematous.

Causes of Bronchopneumonia. In a large proportion of cases, the capillary bronchitis is produced by, or arises as a complication of, one of the acute infective fevers such as measles, whooping-cough, diphtheria, influenza, smallpox, or typhoid and typhus fevers; and it is common especially in children. It may result from the inhalation of irritant vapours or gases, and is a complication in poisoning by chlorine, "phosgene" (carbonyl chloride) or "mustard-gas" (dichlorodiethyl sulphide) (pp. 519–20). Sometimes, acute inflammatory changes in the lymphatics round a bronchus, as is seen in glanders and in influenza, may spread and involve the adjacent lung-tissue, and thus produce patches of bronchopneumonia.

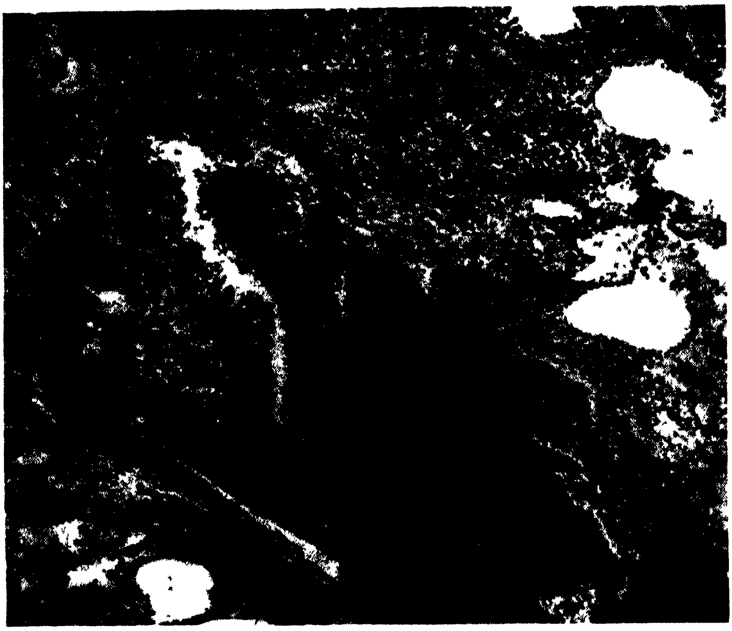

FIG. 312. *Lung.* Acute bronchitis in a case of influenza, showing marked exudation into the lumen and hæmorrhage and œdema into the surrounding tissue. × 75.

The **sputum** is usually mucopurulent, with portions of a rusty appearance, and sometimes streaked with blood. The cellular content is similar to that found in the sputum of lobar pneumonia.

On bacteriological examination, pneumococci and streptococci are found in the great majority of these cases. Other organisms may occur either alone or in addition to these—for example, staphylococci, and the organisms of typhoid fever and plague.

Naked-eye Characters. These vary in different cases. The solid, airless patches are scattered widely throughout the lung-tissue, or are localised to certain parts of the organ. They may become confluent and thus involve a large extent of lung-tissue. Being lobular—*i.e.*, corresponding to lobules or groups of lobules—in their distribution, they are more or less polygonal in shape; and are of a slaty-blue or reddish colour. On section, there is a darker-reddish central part, corresponding to the zone of congestion round the bronchiole ; or the centre may become pale and greyish on account of the accumulation in it of emigrated and degenerating cells. On compressing the lung, little points of yellowish-white muco-pus exude from the smaller bronchi, some of which show acute dilatation of their lumen. The patches of consolidation may be slightly raised above the general surface of the lung, and are commonly surrounded by a zone of acute emphysema. They can often be detected more readily by touch than by sight. When the bronchopneumonic lesions are numerous they tend to coalesce, the intervening lung-tissue becomes œdematous and congested, and the appearance produced comes to resemble that of acute lobar pneumonia. Such "pseudo-lobar" spread is common especially in psittacosis and influenza (pp. 119–20). Usually, however, the section has a somewhat marbled appearance, from the patches being scattered and at different stages of the inflammatory process.

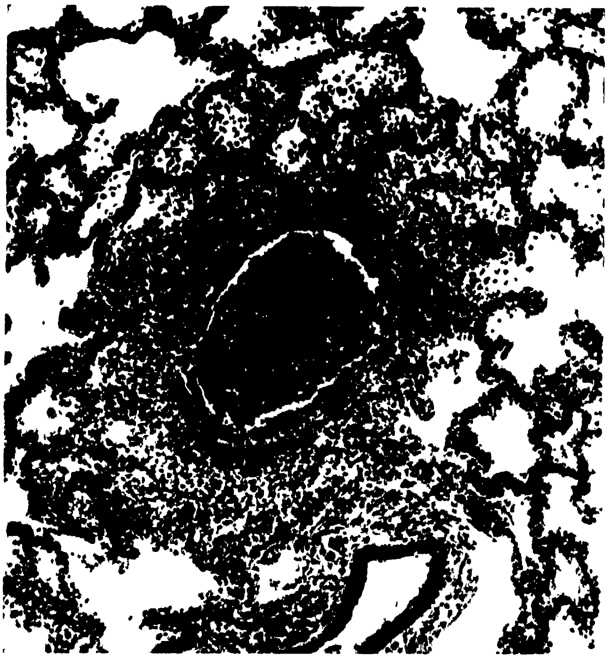

FIG. 313. *Lung.* Showing an area of bronchopneumonia. The lumen of the bronchiole is filled with inflammatory exudate, and there is commencing consolidation of the surrounding air-spaces. × 75.

Microscopical Appearances. When seen in section in the areas of consolidation, the walls of the corresponding intralobular bronchus are swollen and infiltrated with leucocytes, and the lumen is filled with exudate containing desquamated cells, leucocytes, mucoid secretion, granular debris, etc. The neighbouring air-vesicles are consolidated, the cavities being crowded with cells of various kinds, those next the bronchi usually containing, in addition, fibrin. The alveoli may contain red corpuscles in acute cases, but generally the cells present are neutrophil leucocytes with a varying number of mononuclears.

Associated with the consolidation are areas of collapse and of emphysema, exhibiting their usual microscopical appearances. The intervening lung-tissue may show intense congestion and œdema, and the interlobular septa be swollen and œdematous, with evidence of acute pleurisy over the consolidated patches immediately subjacent to the surface of the lung.

Subsequent Changes. The inflammatory products may be absorbed or expectorated, and the lung return to its normal condition. In some cases, however, the collapsed portions remain uninflated, and the peribronchitis may be followed by an overgrowth of fibrous tissue with shrinking and deformity of the lung-tissue. Thickening of the tissues round the minute bronchi and dilatation of the latter are not uncommon, especially in children ; and, in the affected portions of lung, numerous bronchiectatic cavities, usually comparatively small in size, are frequently seen. Thickening of the interlobular septa also occurs. The consolidated parts may become infected with tubercle bacilli. Suppuration and gangrene are uncommon complications, but empyema is not infrequent.

(*d*) **SUPPURATIVE BRONCHOPNEUMONIA.** This may supervene on the preceding non-suppurative type (*c*), and, when occurring in children, the common infecting organism is *Staphylococcus aureus*. Suppuration supervenes in some cases of influenzal pneumonia (*q.v.*, p. 537), and is frequently due to the inhalation into the smaller bronchi of secretions, decomposing materials and foreign bodies containing bacteria. It occurs as **vagus-pneumonia,** where—owing to interference with the vagus or its recurrent laryngeal branch, and consequent paralysis of the muscles which close the glottis—food gains entrance to the bronchi ; or it is found as **aspiration-pneumonia,** where secretions from the mouth or the larger air-passages are drawn into the finer bronchi, as sometimes occurs in surgical operations about the mouth or throat: or as **retention-pneumonia,** where, from pressure upon, or obstruction of, a bronchus by an aneurysm or tumour, by syphilitic stenosis, or by inhalation of a foreign body, *e.g.*, a tooth which has been inhaled during extraction under an anæsthetic, the secretion is retained in the bronchial passages. The food or other foreign body, or the retained secretion, sets up irritative changes in the bronchi, which render them more liable to invasion by bacteria. Catarrh and ulceration, and subsequently—from the spread of the inflammatory processes to the neighbouring lung-tissue—consolidated nodules of broncho-pneumonia, are produced. These appear at first as irregular patches,

FIG. 314. *Lung.* Showing areas of septic bronchopneumonia, following a purulent bronchitis. The lower lobe contains bronchiectatic cavities.

but later coalesce and may resemble lobar pneumonia. Minute points of pus, which look like multiple abscesses, are seen especially in the lower lobes. These may be dilated and ulcerated bronchi filled with purulent secretion or definite abscesses in the consolidated portion. More extensive abscess-formation frequently occurs, and the abscesses, if on the surface, may lead to the production of pleurisy, or may burst into the pleural cavity and give rise to empyema. If the fluids which are inhaled contain putrefactive bacteria, large gangrenous areas are liable to be produced.

The introduction of fats or oils into the respiratory tract leads to a special form of aspiration-pneumonia—**lipoidal pneumonia.** This may arise from aspiration of foods or medicaments of an oily character, but one of the commonest factors in its causation is the use of oily drops or sprays in the naso-pharynx. Somewhat analogous results may follow the intratracheal or intrabronchial injection of radio-opaque preparations such as iodised oils. There is a severe productive reaction in the lungs, and the alveolar spaces may be nearly filled, at least in certain areas, with phagocytes loaded with droplets of foreign lipoid. (For the results of fat-embolism, *see* pp. 169–70 and *cf.* pp. 1029–30.)

(*e*) **INFLUENZAL PNEUMONIA.** In many of the fatal cases, the lungs are solid from an acute hæmorrhagic œdema with little cellular exudation. During life, such patients have a profuse, watery sputum. Usually, however, the consolidation is irregular in type and mainly bronchopneumonic. Though the trachea and larger bronchi and the bronchioles generally throughout the whole lung show extreme inflammatory changes with hæmorrhage Figs. 291–2, p. 506) and even necrosis of the mucous membrane, in the majority of cases the most severe reactions are seen in the capillary bronchioles. There is intense peribronchitis, sometimes with hæmorrhage and œdema, the adjacent lung-vesicles are filled with a cellular and fibrinous exudate, and there is usually an extension of the inflammatory reaction from the bronchioles into the air-vesicles which they supply. The bronchioles themselves may be filled with pus.

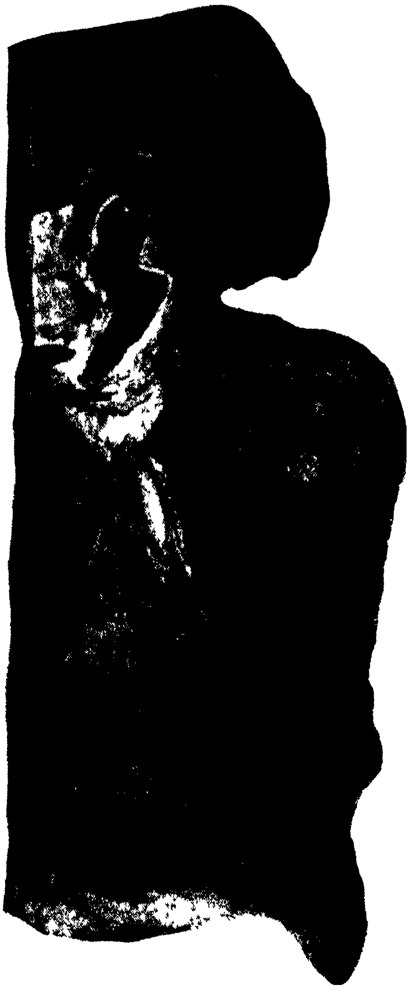

FIG. 315. *Lung from case of influenza,* showing small irregular areas of hæmorrhage, areas of consolidation (pale) and extensive œdema.

The consolidated portions may become confluent and, if they extend to the surface of the lung, pleurisy is developed. The work of the late Sir Patrick Laidlaw and others (p. 120) has established the view that the causal agent is a virus, and that this lowers the resistance of the respiratory tract and thus encourages the multiplication of invading bacteria from the mouth and nasopharynx. Therefore numerous bacteria of various types may be found in the inflamed regions—streptococci, staphylococci, pneumococci, Gram-negative cocci of the *M. catarrhalis* group, and the bacillus of Pfeiffer.

Sequelæ and Complications. Lobar pneumonia may be superadded. The purulent condition in the bronchioles may extend to the consolidated patches, producing a suppurative pneumonia with abscess-formation and empyema. A commoner sequel is interstitial pneumonia. A commencement of this fibrous change may be seen, even in the acute stage of the disease, in the region of the peribronchitis and, later, its spread in the lung-tissue can be traced. The absorption of the inflammatory products in the lung and in the bronchi is usually delayed, with resulting organisation, increase of fibrous tissue and collapse of those portions of lung connected with the fibrosed bronchus. The invading organisms of secondary infection may give rise to septicæmia. This is commoner during epidemics.

(*f*) **PSITTACOSIS.** In this disease, caused by a filtrable virus derived from diseased parrots and other birds, the lung-lesion is a bronchopneumonia somewhat similar to that of influenza. (*See* under Viral Diseases, p. 119.)

(*g*) **VIRAL PNEUMONIA or VIRAL PNEUMONITIS.** During the past few years, the occurrence of small epidemics of an apparently **virus-produced form of pneumonia,** in some ways resembling, but distinct from, the pneumonias of influenza and psittacosis, has been described in America—though the earliest report of the condition was published from Hawaii by A. Bowen in 1935. Longcope[1] (1942) sums up the pathological findings in the lung as: "a hæmorrhagic broncho-pneumonia, with red blood cells, mononuclear cells and coagulated fluid in the alveoli," and he adds that: "The etiological agent appears to be a virus, which is not the influenza virus. The disease is not affected favourably by sulphonamides or known derivatives." About half the cases are "mild," a quarter are "moderately severe," and the remaining quarter "in such violent form that death may occur" (as in three out of the ten "very severe" cases in his own series of patients). There is racking cough, with little or no expectoration—the examination of any sputum obtainable being "negative" for ordinary bacteria: high fever: moderately slow pulse: absence of leucocytosis (and perhaps a leucopenia) in the early stages: a prolonged febrile course, with termination by lysis, not crisis: and the X-ray shadows in the lungs, especially in the lower lobes, being more pronounced than might be expected from the physical signs. Complications are not numerous, and recovery is the rule.

(*h*) **ABSCESS OF THE LUNG.** As already stated, the consolidated patches of septic bronchopneumonia (Fig. 314) may become softened and purulent, but definite abscess-formation occurs more frequently in pyæmia arising, for example, from septic thrombosis of the uterine and other veins in puerperal conditions, or of the various intracranial venous sinuses in middle-ear and other diseases of the bones of the skull. In these instances, the lung-abscess originates as a septic infarction. Similar abscesses may originate from septic emboli carried from the vegetations on the pulmonary or tricuspid valves in septic endocarditis. In suppurative periostitis and in osteomyelitis, bacteria may be carried to the lungs and there give rise to multiple abscesses. Around these, the lung-tissue is intensely congested and œdematous, and often hæmorrhagic. Abscess of the lung may also follow the inhalation of a tooth or tooth-fragment, or other septic foreign body. **Microscopically,** the condition is seen to be a hæmorrhagic catarrhal pneumonia in which suppuration supervenes. Embolic abscesses are usually multiple, vary in size from minute points of suppuration up to large abscesses, and the pleura over them may show acute inflammatory changes. Rupture into the pleural sac, giving rise to empyema, or more commonly to a pyo-pneumothorax, may take place, or the abscess-cavity may burst into the bronchi. Greenish-yellow pus, often in considerable amount, and containing fragments of lung-tissue, is a constituent of the sputum in such cases. In some very acute cases of osteomyelitis, the autopsy shows only numerous minute hæmorrhagic areas throughout the lungs, with no naked-eye evidence of the presence of suppuration ; but, in microscopical sections, plugs of staphylococci are found both within and around the capillaries. In such cases, death has taken place before suppuration has developed sufficiently to produce definite abscess-formation.

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[1] "Pneumonitis or Virus Pneumonia," by Warfield T. Longcope, Physician-in-Chief, Johns Hopkins Hospital, Baltimore, *Practitioner*, 1942, **148,** 1.

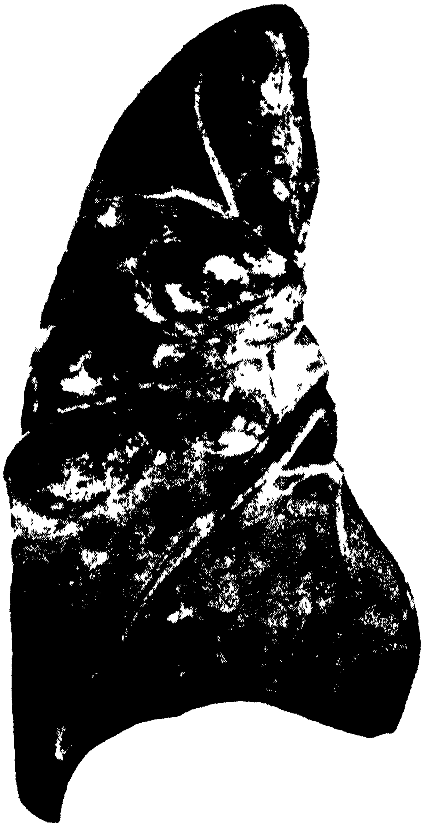

FIG. 316. *Lung* of a male aged 37. Septic bronchopneumonia and multiple abscesses.

GANGRENE OF THE LUNG :—

This condition results from the action of putrefactive organisms upon damaged or dead lung-tissue. It may be due to the direct extension into the lung of necrotic and ulcerating lesions of the œsophagus, the stomach, or the bones of the chest-wall : to putrefactive material inhaled from ulcerative and necrotic processes in the mouth and upper air-passages : or to putrefactive changes in the secretion which accumulates in the bronchi as a result of obstruction by the pressure of tumours or aneurysms. The infective material sometimes reaches the lung in the form of emboli ; but gangrene will result only if, in addition to the pyogenic organisms present in the emboli, putrefactive organisms have gained access to the damaged lung. In diabetes mellitus and in chronic alcoholism, pneumonia not uncommonly terminates in gangrene.

Morbid Anatomy. The gangrenous areas become soft and putty-like in consistence, dark red or green, or almost black in colour, and usually have a very foul odour. The surrounding tissue is intensely congested, it may be consolidated, and is often extremely œdematous. Invasion of the bronchi is common, and the expectoration is profuse, mucopurulent, of a yellowish or brownish colour, generally intensely fœtid, and may contain shreds of necrotic lung-tissue, desquamated alveolar cells, often with included pigment, fatty-acid crystals, and fat-droplets. Masses of various kinds of bacteria, including leptothrix-filaments, are found. In some cases, where death does not occur, the whole of the gangrenous tissue-debris is discharged through the bronchi, and the cavity may become gradually filled by granulation-tissue. Thus, repair is effected, and, at a later period, an irregular scar is the only sign of the original gangrenous area.

HYPOSTATIC PNEUMONIA :—

Reference has already been made to hypostatic congestion and œdema of the dependent parts of the lungs (p. 521). Consolidation may follow and a subacute form of inflammation of the terminal bronchioles and air-vesicles be set up, and, in this way, these become filled with catarrhal cells and with fibrin and leucocytes.

INTERSTITIAL PNEUMONIA :—

The disease, although sometimes acute, is generally subacute or chronic and then results from continued irritation, and may involve larger or smaller areas of lung-tissue, and is characterised by an overgrowth of the connective-tissue framework of the lung ; and this may give rise to secondary changes in the bronchi, lung-tissue and vessels.

Classification. Several varieties, the special characters of which are dependent largely upon the different causal factors at work, are found. The most important are :—

1. Those which are the result of the action of bacterial and other organismal infections, *e.g.*, the interstitial pneumonias of tuberculosis, syphilis, leprosy, glanders, and influenza.

2. Those which follow acute or subacute conditions of the lung or pleura, as, for example, imperfectly-resolved acute lobar or lobular pneumonia, collapse, irritation of a foreign body, vagus- and retention-pneumonia and pleurisy.

3. Those resulting from the inhalation of dust or other foreign particles (the **Pneumonokonioses**). The most familiar examples are the diseases produced by the irritation of coal- or stone-particles in coal-miners, stone-cutters, and grinders.

Microscopical Anatomy. The different varieties of interstitial pneumonia exhibit certain common features. The connective-tissue overgrowth always commences in positions in which the original connective tissue is most abundant, and gradually invades the lung, encroaching upon, altering, and obliterating large tracts of the smaller bronchi and the aerating tissue. The starting-points of this overgrowth are usually the deeper layer of the pleura, the interlobular septa, and the connective tissue round the bronchi and the vessels. In the more acute varieties which occur in influenza and in glanders, the peribronchial and the perivascular tissues especially are those which show proliferative changes ; whereas, in the more slowly-produced forms due to dust-diseases, the overgrowth is mainly in the deep layer of the pleura and in the interlobular septa.

The proliferated connective tissue varies in its character in the different forms. It may be dense and show little evidence of cellular growth, or the cellular character may be pronounced. The degree of vascularity varies considerably. The bronchi may become dilated during the more active or acute stage, and this dilatation may persist, or even be increased later. The secretion may be retained, undergo decomposition, and lead to still further dilatation and the production of a condition of bronchiectasis. During the progress of this fibrosis, the cells lining the alveoli alter in character, become more cubical or spheroidal, and simulate those of gland-tissue or of the embryonic lung. This alteration may be seen in any of the forms of interstitial pneumonia, and is a stage in the obliteration of the alveoli. This cubical or even almost columnar type of cell may be abundant, and the appearance produced may easily be confused with that seen in an adenocarcinoma.

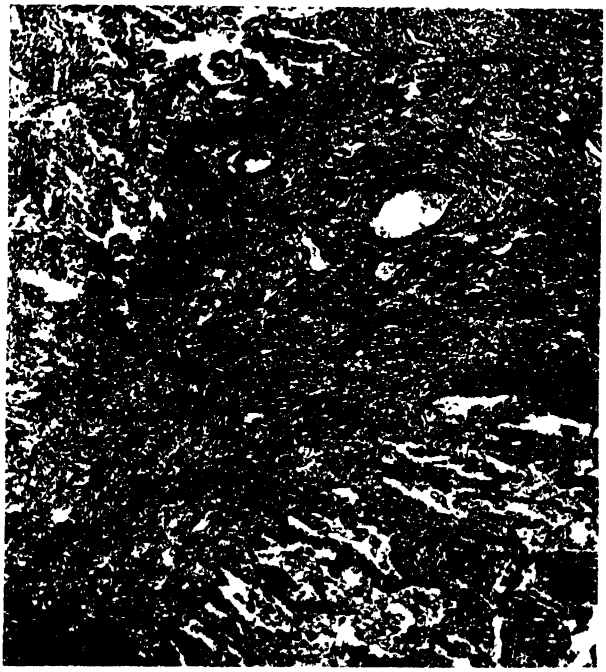

FIG. 317. *Lung.* Interstitial pneumonia, showing great increase in dense fibrous tissue. × 50.

1. **The Forms of Subacute and Chronic Interstitial Pneumonia which result from the Action of Bacterial and other Poisons or Toxins.** In all these forms there is an increase in the fibrous tissue in the lungs, varying, however, in distribution and in its stage of development. In **influenzal** pneumonia, the fibrous tissue may be patchy in its distribution and so cellular in its character, as to be regarded as an **acute interstitial pneumonia.** The cellular proliferation is shown

principally in the interlobular septa which become thickened, and from these septa extension takes place into the lung-tissue. There is usually also associated peribronchitis. In **syphilis** and **tuberculosis** (pp. 87 and 560–1) the causal organisms are relatively slow in their action on the tissues and the proliferative lesions are less cellular, and in most cases predominantly fibrous. In **chronic glanders** (pp. 89–90) the new fibrous tissue is produced mainly by proliferation of the peribronchial and perivascular connective-tissues.

FIG. 318. *Lung.* Anthracosis, a characteristic example of "coal-miners' lung."

2. **The Forms of Interstitial Pneumonia which follow Acute or Subacute Diseases of the Lung.** Reference has been made (pp. 532, 536 and 538) to the organisation and subsequent fibrosis of the unabsorbed exudate in some cases of acute lobar pneumonia and bronchopneumonia. This is a reparative process, and the fibrous tissue may occur in localised patches, or be widespread throughout the lung—the new fibrous tissue developing from the pleura, from the septa, or from the peribronchial and perivascular connective tissues, and being cellular in its early stages.

3. **The Pneumonokonioses**[1] (*q.v.*, pp. 231–233). The results of the inhalation of dust depend largely on the character of the particles inhaled. Thus, that part of the fine dust of the air which is not expectorated is taken up from the channels and cavities of the lung into the lymphatics, and is deposited in various situations, but does not necessarily give rise to any serious damage If the dust is of an irritating character, it causes reactive changes, with the production of nodules of fibrous tissue in the sites in which it is deposited (the deeper layer of the pleura, the interlobular and interalveolar septa, and the peribronchial and perivascular lymphatics). The dense nodules thus formed show a homogeneous central fibrous area surrounded by a zone of pigment mapping out the position of the peribronchial lymphatics.

According to the nature of the dust inhaled, various names have been given to the lesions produced.

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[1] Greek, κονία or κόνις, *konia* or *konis*, dust.

(*a*) **ANTHRACOSIS**[1] (**" Coal-miners' Lung "**) is due to the inhalation of particles of coal-dust. These carbon-particles have, in themselves, comparatively little irritating action, but they may be associated with the more irritating particles of stone or silica, and the small white fibrous areas seen on the surface of the lung in anthracosis are produced by the silica. Owing to this combined action of carbon and silica in producing both pigmentation and fibrosis, the term **silico-anthracosis** is sometimes used to describe the mixed condition, which is found especially in miners working with hard-coal (anthracite) or with coals much mixed with ordinary stone. The lungs are usually voluminous and emphysematous and the bronchial lymph-nodes show masses of carbon-pigment. The lung becomes intensely black, and the pleural surface usually shows some small irregular, white, fibrous areas, surrounded by a darker zone of pigment. Under these fibrous areas, gritty particles may be felt. The cut surface is also finely gritty.

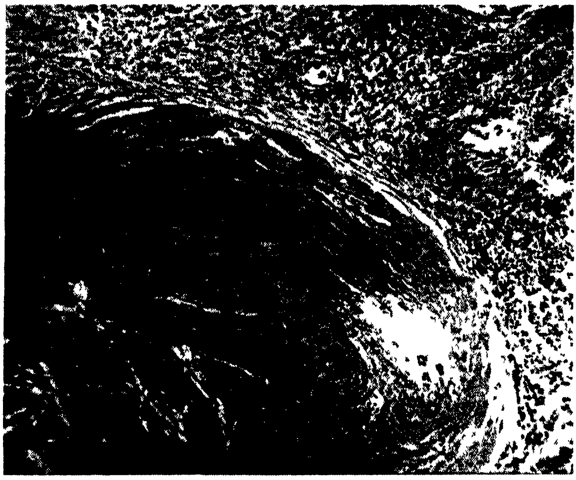

FIG. 319. *Lung.* Silicosis, showing the concentric arrangement of the fibrous tissue in, and the progressive fibro-cellular zone at the periphery of, the nodule. × 70.

FIG. 320. *Lung.* Silicosis showing a typical nodule from the lung of a grinder. There was no evidence of tuberculosis in this part of the lung. Note the dense fibrous-tissue nodule with homogeneous centre and blackish pigment, especially round the central area. × 40.

On microscopical examination, large aggregations of black pigment, in the form of fine granules, are seen in the connective tissue, which is often almost obscured by them. The bronchi and alveoli generally show catarrh, and the lung-tissue may be congested and contain many carbon-laden phagocytes.

(*b*) **SILICOSIS (Chalicosis or " Stone-Masons' Lung ")** is due to the inhalation of stone-particles, or particles of glass or quartz. Only certain kinds of stone produce the irritation, especially those containing high percentages of silica, such as quartz-rock, granite and flint. The degree of fibrosis and the time taken for its development vary according to the concentration of the dust in the atmosphere, the daily, as well as the total, duration of exposure, and the size of the inhaled particles. Sayers and R. R. Jones[2] (1936) state that particles measuring up to $10\,\mu$ are capable of being engulfed by phagocytic cells and of entering the finer air-spaces. The most effective absorptive results, however, are obtained with those measuring 1 to $3\,\mu$. The fibrous nodules formed in silicosis are usually fewer in number than in anthracosis, and, on account of the more irritating nature of the particles, are larger and denser in consistence. Destructive changes are also more pronounced. Owing to the obliteration of the vessels at the periphery by endarteritis or by thrombi which have become organised, the central part of the nodules often shows necrosis.

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[1] For derivation, *see* footnote on p. 505. Galen used the term ἀνθράκωσις, *anthrakōsis*, for " a dark-coloured malignant ulcer," and not in connection with the lung.

[2] R. R. Sayers and R. R. Jones, " Silicosis and its Control," *Surgery, Gynæcology and Obstetrics*, 1936, **62**, 464.

Gye and Kettle (1922), as a result of various experiments, state that silica causes fibrosis by acting chemically on the tissues, and not merely in virtue of its physical properties. In their experiments, they reproduced, not only the fibrous changes, but also the necrosis, which is so prominent a feature of silicosis. They consider that this necrosis is caused by a soluble derivative of silica which acts as a cell-poison; and that the fibrosis, though partly reparative, is due largely to the irritative action of colloidal silica into which the inhaled dioxide of silicon has been converted in the tissues.

Although it is not yet proved, it is generally accepted that it is the dioxide of silicon that is chiefly responsible, though some silicates have a similar action, and certain workers maintain that a special silk-like silicate (sericite, a potash-mica), is similarly capable of producing these changes.

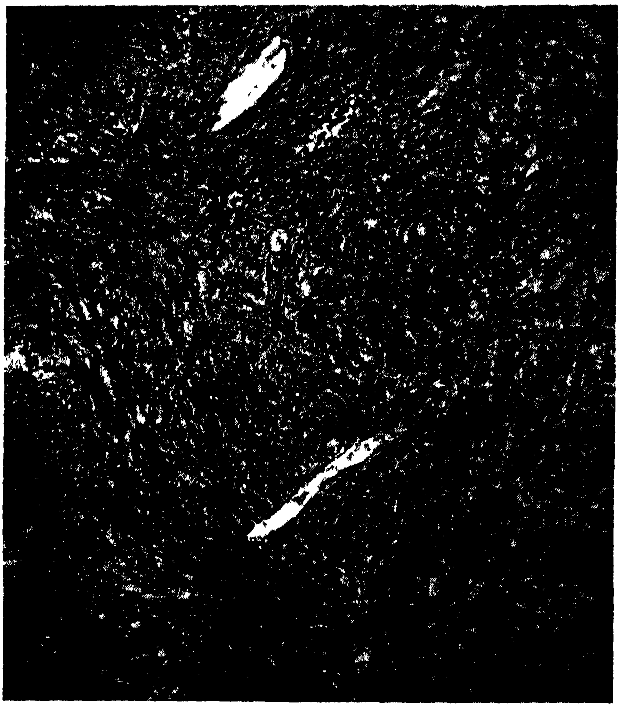

FIG. 321. *Lung.* Silicosis, showing a fibro-cellular stage in the development of the silicotic nodule and the almost complete obliteration of the lung-alveoli. From the lung of a knife-grinder. × 100.

It has been shown by one of us[1] that, if guineapigs are exposed for varying periods to the inhalation of stone-dust with a high silica-content, a pronounced cellular or fibro-cellular proliferation takes place, with obliteration of the air-cells, a condition similar to that seen in the advancing edge of silicotic nodules in human cases. The proliferated connective-tissue cells are often loaded with the particles of stone-dust. No evidence of a primary necrosis was present in these experimental animals (Figs. 322 and 323).

On naked-eye examination, the lung in silicosis has a greyish colour. In the pleura, the whitish fibrous nodules to which reference has already been made under anthracosis, are much more marked, larger, and more numerous. On the cut surface, the gritty stone-particles can be felt under the finger, and are seen to be surrounded by pigmented fibrous tissue.

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[1] In these experiments, the dust-concentration was high, and the silica-content from 80 to 90 per cent. The dust used was the fine particles deposited in ridges and irregularities in the higher parts of the local quarries. Before introduction into the inhalation-chambers, it was passed through a sieve of very small mesh. (J. M. Beattie, unpublished.)

On microscopical examination, dense nodules of fibrous tissue are found, often homogeneous and necrotic in the centre, and containing minute angular or irregular particles of a greyish-black colour—the stone-dust. Catarrh, congestion, and emphysema of the intervening lung-tissue are commonly present. The vessels at the periphery of the nodules may show obliterative endarteritis, and the connective tissue in this situation is more cellular and vascular than in other parts of the lung. Tuberculosis is frequently associated with silicosis, and the destructive changes in such cases may be considerable.

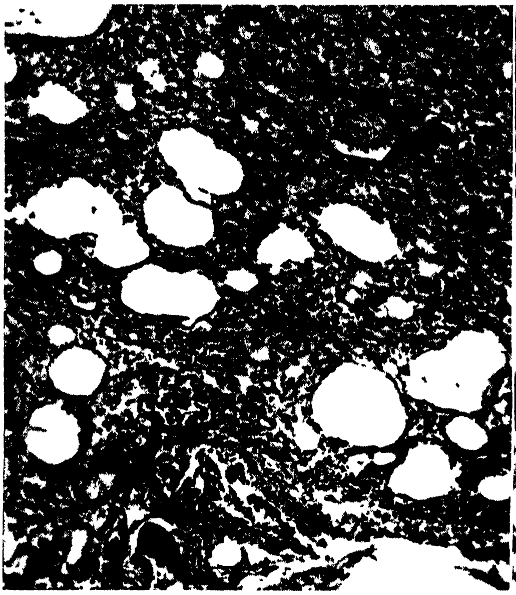

Fig. 322. *Lung* of a guineapig in experimental silicosis, showing cellular proliferation with associated obliteration of lung-alveoli. The cells contain numerous particles of stone-dust. Compare with Fig. 324. × 70

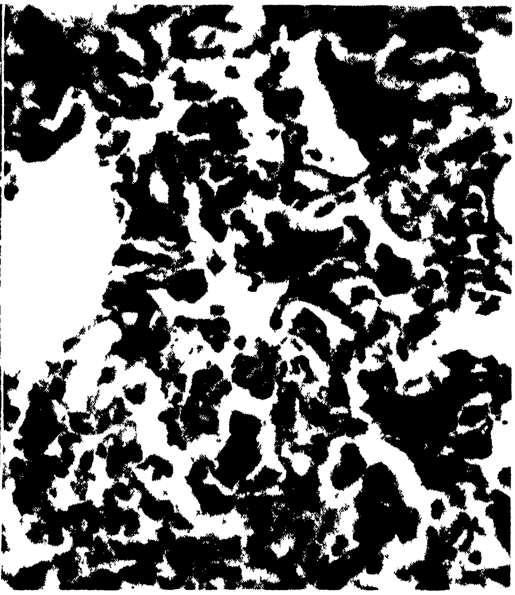

Fig. 323. *Lung* of a guineapig which had been exposed, at intervals for one month (actual total exposure eight hours), to a concentrated dusty atmosphere with a high content of silica. The section shows proliferated connective-tissue cells (many of which are filled with stone-dust) and obliteration of lung-alveoli. Compare with Fig. 325. × 300.

Gye and Kettle explain the prevalence of tuberculosis among silica-workers by, firstly, the destructive action of colloidal silica on cells, whereby foci of necrosis are produced, the tissue-resistance broken down and the growth of the tubercle bacillus encouraged : and, secondly, the disorganisation of the lymphatic drainage of the lung. From experiments by Leroy U. Gardner,[1] " it would appear that the tubercle bacilli multiply in areas where a sufficient quantity of silica-particles has accumulated. But the mere presence of the silica is not the only essential ; the mineral must have had time to act on the tissues and produce an appreciable amount of necrosis." These experiments confirm the view of Gye and Kettle. Contrasted with the commoner chronic forms of the disease, a more rapidly-developing or so-called "**acute silicosis**"[1] may be found among abrasive-soap workers and in those engaged in crushing quartz to a fine powder and in sand-blasting, if not suitably protected against the inhalation of the dust. These workers are liable to develop a nodular fibrosis of the lungs which may run a fatal course in as short a period as a few months and often complicated by tuberculosis. The nodules are small, perhaps only microscopic, and Belt[2] (1939) states that similar silicotic nodules may be found in the spleen.

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[1] " Silicosis and Asbestosis." Edited by A. J. Lanza. Oxford University Press, 1938 : Section V, " Experimental Pathology," by Leroy U. Gardner, p. 335.

(*c*) "**GRINDERS'**" or "**TURNERS'**" **LUNG,** often called **Siderosis.** Many authors lay stress on the damage done by iron- and steel-particles in the lungs of needle-grinders, file-makers and knife-grinders. Though the particles of steel must produce an irritant action, this view, which has been handed down in various textbooks, has very little evidence to support it. The experience of one of us (J. M. B.) among the grinders in Sheffield is that the dust from the grindstone is the main causal factor in so-called "grinders' phthisis," and that it is silicosis, and not siderosis, from which these workers suffer. The changes produced are identical with those seen in the silicosis of stone-cutters. Tuberculosis is a very common complication in the grinders' lung, at all events in Sheffield, and, in many cases, it is the cause of death. A definite interstitial pneumonia does, however, occur in grinders' lungs without tuberculosis. Hypertrophy followed by dilatation of the right side of the heart and venous congestion and œdema of the lungs are evident in many cases of "grinders' phthisis," and death from cardiac failure is not uncommon.

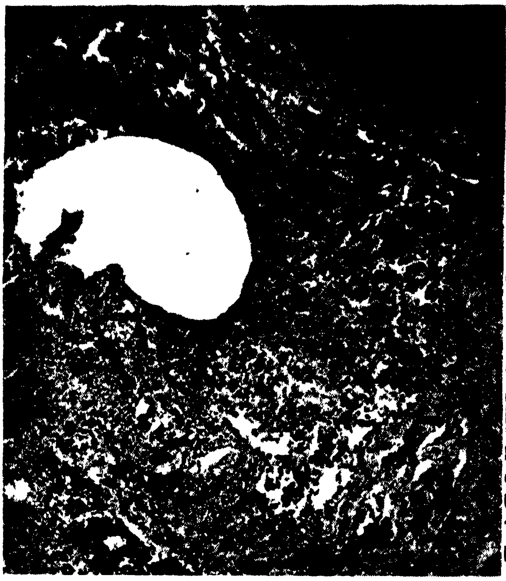

FIG. 324. *Lung.* Silicosis in a scissor-grinder, showing a fibro-cellular zone surrounded by dense fibrous tissue and dark pigment. One alveolus is distended, others, at lower right-hand corner, are almost obliterated. × 100

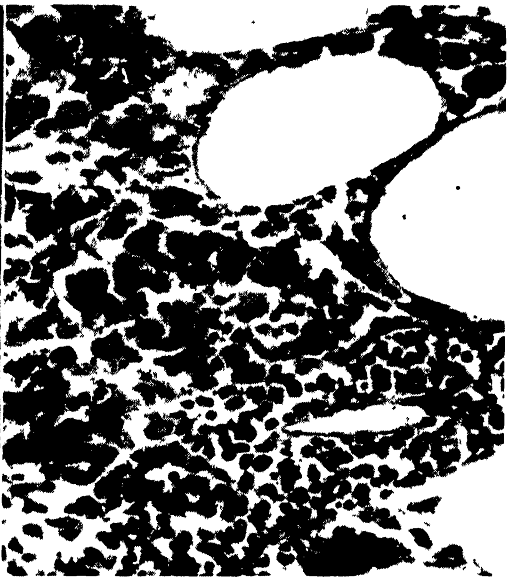

FIG. 325. The same under a higher power, showing the cellular proliferation, and the stone-particles in many of the proliferating cells. × 300

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[1] "Rapidly Developing Silicosis," *Lancet*, "*Annotation*," 1941, *i*, 422.

[2] T. H. Belt, British Postgraduate Medical School, "Silicosis of the Spleen," *Jour. Path. and Bact.*, 1939, **49**, 39.

(*d*) **ASBESTOSIS.** This is a form of silicosis, the irritating substance being magnesium silicate. Gloyne[1] (1938) states that, in asbestos-workers, the asbestos-fibres can be found in the nose and throat and occasionally in the conjunctival sac, and that, in cases coming to autopsy, histological examination of the walls of the larynx, trachea and large bronchi usually reveal no lesions of asbestosis. When the lungs are affected, the disease appears as a diffuse fibrosis, especially of the lower lobes. Emphysema and bronchiectasis are commonly present, and the pleura is thickened and usually adherent to the diaphragm.

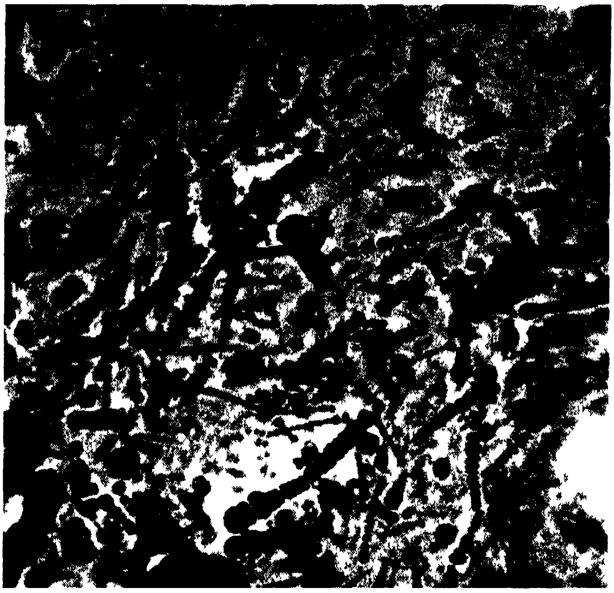

FIG. 326. *Lung.* Asbestosis bodies in sputum from an asbestos worker × 700.

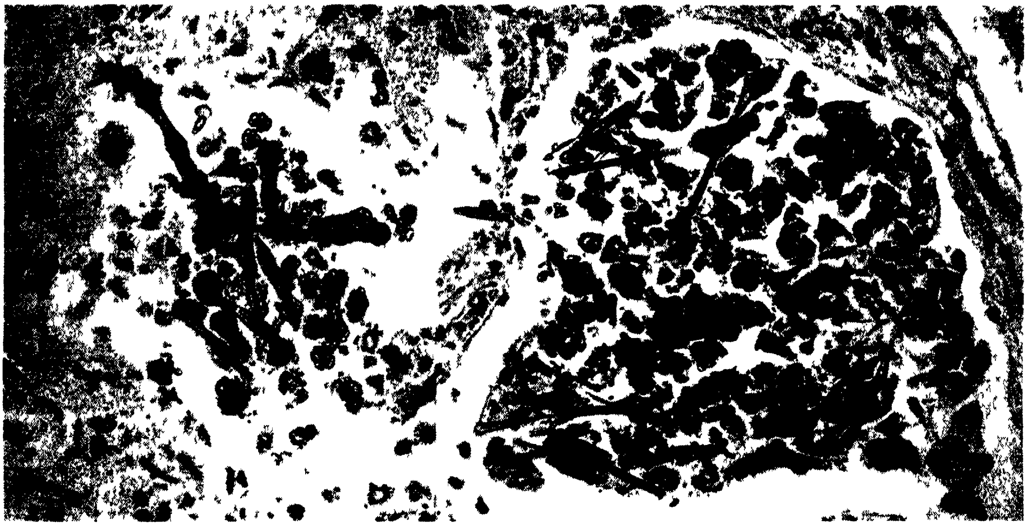

FIG. 327. Asbestosis-bodies in section of lung from another case. × 350. (By courtesy of Dr. Norah Schuster.)

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[1] "Silicosis and Asbestosis." Edited by A. J. Lanza. Oxford University Press, 1938: Section IV, "Pathology," by S. R. Gloyne, p. 199 *et seq.*

Scattered in the fibrous tissue, in the alveoli and in the dilated small bronchi, " asbestosis bodies " are found. These are thin, tapering structures with bulbous extremities, transversely ribbed, suggesting that they are composed of a series of apposed disks. They are of a golden-yellow or brown colour, and give a reaction for the presence of iron with ferrocyanide of potassium and hydrochloric acid. Each consists of a central filament coated with some organic deposit from the tissues. By some writers the iron-reaction is regarded as due to the presence of a hæmoglobin-derivative rather than to the iron which is combined with the magnesium in the fibrous silicate, causal of the fibrosis. In the lung-tissues, groups of these bodies may be seen surrounded by phagocytic cells. They can, and in small numbers do, occur in the sputum of some of those exposed to the asbestos-dust, but, as pointed out by Matthew Stewart, this is not of necessity accompanied by involvement of the lung itself. If, however, they occur in the sputum in clumps or masses, this is an indication that they have come from breaking-down lung-tissue. Tuberculosis, though not so frequent as in silicosis due to stone-dust, is often associated with asbestosis.

FIG. 328. *Sputum in asbestosis.* High power of fresh-wet film of sputum of Dr. Norah Schuster's case, showing a group of "asbestosis-bodies," with their characteristic " clubbed " or " chicken-bone like " formation—some also resembling a clove in shape—around the central fibre. In some the typical transverse markings or fissures are also seen. × 400.

(*e*) **Workers with flax, feathers, clay, porcelain, oxide of iron, plasters, pigments,** etc., are said to develop varying degrees of interstitial pneumonia. In many of these workers, the changes are slight and unimportant; but in others, such as potters, they are more pronounced and are due to the irritating dust of flint or silica in some combination. In hæmatite-workers, the fibrosis is more cellular, more diffuse and less nodular than in silicosis, and the lung is a rusty-brown colour from the deposit of iron. Silica is also present, and the fibrosis is due probably largely to its action. This condition is a **siderosis** or, more correctly, a **silico-siderosis.** Workers employed in making cardboard from broken and crushed **sugar-cane** after the sugar has been extracted ("**bagasse**"), and which contains some five per cent. of silica, also suffer from a dust-disease of the lung.

(*f*) The use of **metallic magnesium** in the form of fine powder for many war-time purposes (flash-light photography, the making of flares and incendiary bombs, etc.) has added yet another form of pneumonokoniosis to those already recognised ; and workers with magnesium are also, from the employment of bichromate solutions in the industry, exposed to the danger of chrome-poisoning, chrome-dermatitis and nasal ulceration (p. 245).

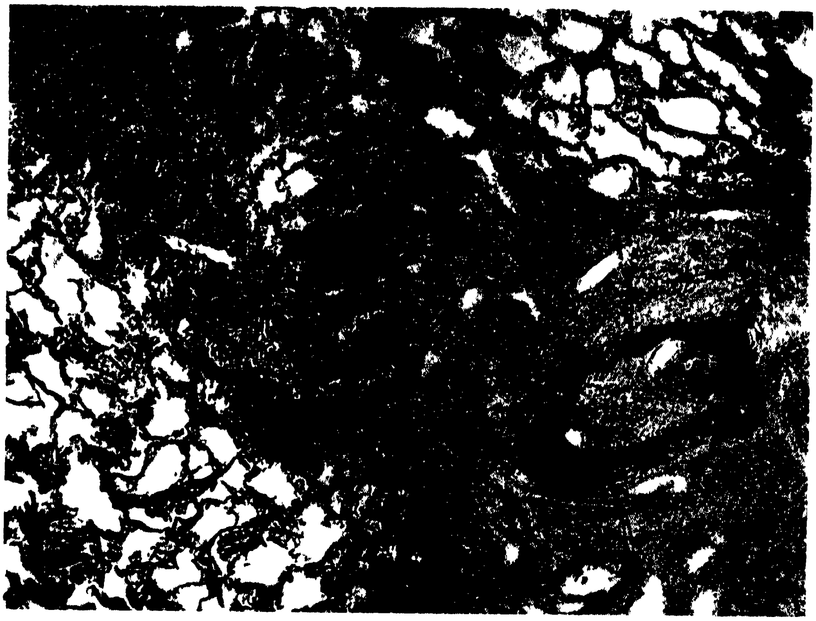

FIG. 329 *Lung*. Syphilitic interstitial pneumonia, The elastic tissue is stained black by Weigert's method. Note obliterative endarteritis in vessel. × 28.

The Forms of Acute Interstitial Pneumonia which result from the Action of Bacterial and other Poisons or Toxins. Occasionally, an acute interstitial pneumonia resembling the pleuro-pneumonia of cattle is seen. In this, the principal change is in the interlobular septa, which become thickened, and from which extension takes place into the lung-tissue. Usually, there is also

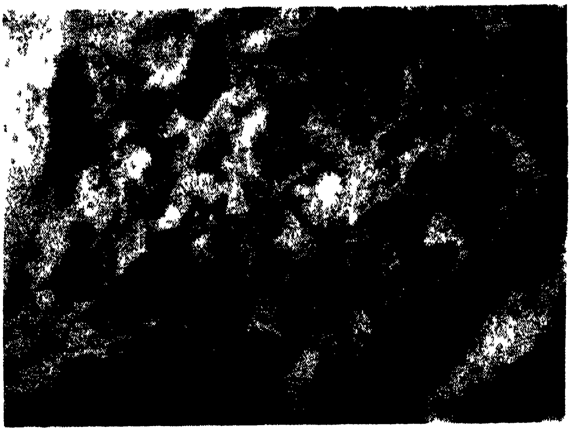

FIG. 330. *Fœtal lung* from a case of congenital syphilis, showing numerous spirochætes. Levaditi's silver-impregnation method. × 850.

an associated peribronchitis. This condition is seen especially in some of the cases of pneumonia which are associated with **influenza** (p. 537). The "white pneumonia" of **congenital syphilis** is really a form of interstitial pneumonia resulting from the presence of enormous numbers of spirochætes and the *formation of a large amount of cellular fibrous tissue (Figs. 329, 330). A more detailed description of this lesion and of the other syphilitic manifestations in the lungs is given in Chapter III, p. 87.*

In **Glanders** *and in* **Actinomycosis** *(pp. 89, 91 and 568*A*), the fibrous overgrowth which takes place in the lung is secondary to the more acute lesions of softening and abscess-formation. In actinomycosis, the fibrosed tissue is really the scar-tissue of the healed abscess and may occur at any part of the lung ; but,* in glanders, the new tissue generally arises by a proliferation of the peribronchial and the perivascular connective tissues. Other *Streptothrices* (pp. 92 and 568A), *e.g.*, *Actinomyces* (or *Streptothrix*) *asteroides* of Eppinger, sometimes produce minute abscesses scattered throughout one or both lungs which may simulate acute miliary tuberculosis.

SECTION IV

TUBERCULOUS DISEASE OF THE LUNGS AND PLEURA

Tuberculosis in the lungs may be part of a more general process (p. 55 *et seq.*), or it may be localised in the lungs. All forms are caused by the presence of *Mycobacterium tuberculosis* ; and the differences in the lesions depend on various factors, such as the channel of infection, the method of spread in the lung and the special structures involved, the type and virulence of the organism and the power of resistance of the patient, the presence or absence of previous disease and damage in the lung, and the supervention of intercurrent processes, especially secondary infection with other organisms.

Though no essential pathological difference exists between tuberculosis with cavitation and tuberculosis without any evidence of cavity-formation, yet, in the study of tuberculosis of the lung, we think it advisable, in the interests of clarity, to make this artificial distinction. Hence the classification which follows.

Classification :—

(A) **Tuberculosis, without Cavity-Formation.**

I. **Acute** :

1. Infection by blood-stream.
2. Infection by lymphatics.
3. Infection by way of the air-passages. This gives rise especially to acute caseating tuberculous bronchopneumonia.

II. **Chronic.** This form is due to spread mainly by the peribronchial lymphatics.

(B) **Tuberculosis with Cavity-Formation (Phthisis).**

I. **Acute** : which is mainly bronchopneumonic in type.

II. **Chronic** : which is seen principally in the peribronchial lymphatics.

General Facts in Relation to Tuberculosis of the Lungs :—

Most of the cases of pulmonary tuberculosis in man are caused by the human type of the bacillus ; but in some countries and in certain localities the incidence of infection by the bovine type may reach 20 to 30 per cent. There is great variation in the rapidity, *i.e.*, the acuteness or the chronicity, of the process, and, therefore, in the resulting lesions. Thus, the more acute the disease, the greater the tendency to caseation and destruction : the more chronic, the greater the amount of fibrous-tissue overgrowth. The lesions in the lung during the course of the disease depend largely on the relative proportion of these two processes to one another. As already stated, they may be part of a general tuberculous infection throughout the body, as, for example, in the acute miliary tuberculosis produced by inoculating animals : or that found in children : or in older patients with weak resisting power. On the other hand, the infection may start in the lungs, and from them be carried to other parts of the body ; or the lung may become infected from some focus of the disease elsewhere. In the child, the primary lesion in the lung, described by Parrot (1876), and Kuss (1898), and confirmed by Ghon, (1912), and called the "**Ghon-lesion,**" is usually a small caseous area of bronchopneumonia, subpleural in position and present in the lower part of the upper or

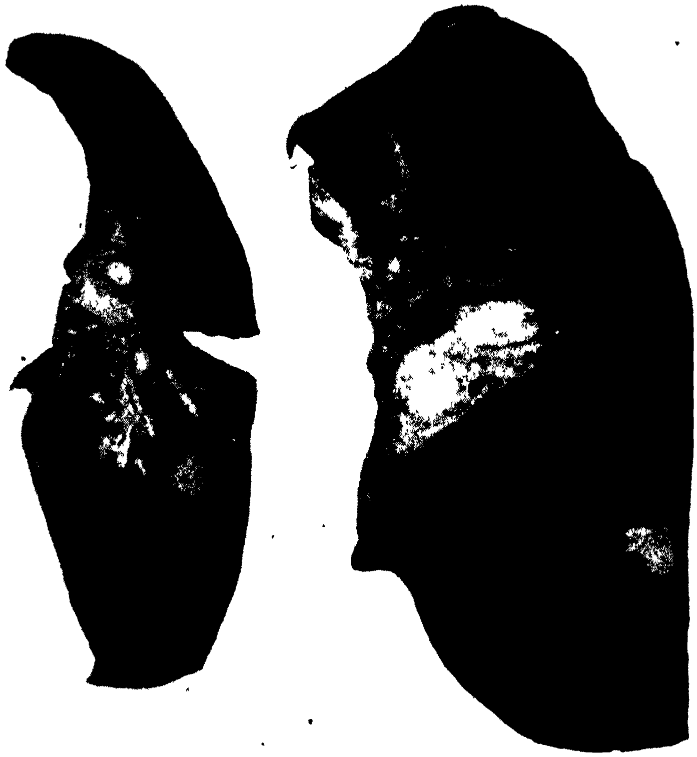

FIG. 331. *Lungs* of two children, each showing a primary focus (" Ghon-nodule ") in the lower lobe and infection of the glands at the root.

in the lower lobe. From this site the spread may be traced to the corresponding lymph-nodes at the hilum of the lung. A similar sequence of events may be found in adults, but, as a rule, the first clinical evidence of pulmonary infection in the adult appears at the apex, but this is generally secondary to tuberculosis in some other organ or tissue, and is lymphatic in distribution. Both lungs are almost always attacked, but the disease is usually more pronounced on the right than on the left side. It is, however, not uncommon to find at the root of the lung what appears to be a primary focus of infection. Lesions resulting from other diseases, *e.g.*, Silicosis (p. 543 *et seq.*), may modify the pathological picture.

When the tubercle bacillus has obtained access to the tissues, it tends to persist in the local lesion and also to spread progressively, unless a cure is effected. There is also the possibility that re-infection from outside may be taking place intermittently, *e.g.*, from the close association of members of a family with one who is infected, or of nurses in a hospital with tuberculous patients.

The presence of simultaneous proliferative and destructive changes in the lungs probably explains the slow development of the disease in many patients ; but this slowly progressive character, so typical of the disease in adults, as compared with the rapid advance in children, is generally ascribed to a state of immunity in the adult brought about by an early infection or series of infections of a low grade of intensity in the lungs, the alimentary tract, the lymph-nodes or elsewhere—a process sometimes described as " subinfection " or " subclinical infection." A belief in this hypothesis has suggested to various observers the possibility of immunising children by inoculations of dead bacilli or of living organisms of low virulence (p. 64).

Methods of Infection :—

There is general agreement that, in young children, one of the channels of entrance of the tubercle bacilli is by way of the tonsils, and the lymphoid tissue of the pharynx, and, in some cases, by way of the nose or teeth, but it is doubtful whether by these channels a direct lung-lesion is produced. It is more probable that the bacilli pass from these situations to the cervical, then to the mediastinal and bronchial lymph-nodes, and finally into the lung-tissue by way of the peribronchial lymphatics of the larger bronchi.

In children, a primary infection of the lung (the " Ghon-lesion," see p. 551), with secondary involvement of the tracheo-bronchial lymph-nodes, is not infrequent. These primary lesions are found at the periphery of the lung, just under the pleura, and the method of infection seems to be the inhalation of tubercle bacilli directly into the lung. This primary lesion and the associated tracheo-bronchial lymph-nodes undergo caseation, and invasion of and destructive changes in the lung may follow. According to American workers, healing of the primary lesion is not uncommon. It may become encapsuled and calcified. Blacklock's experience in Glasgow is that, in children under three years of age, a rapid spread takes place within a short time of the onset, with a fatal result either from extensive destructive changes in the lung or from tuberculous meningitis. He considers that healing in children of that age, at all events in Glasgow, is rare. In adults, the inhalation of the bacilli in dust or in air-borne droplets or dried-up fragments of sputum is the principal mode of infection. Usually the bacilli are carried into the bronchi. They may become lodged there, or, what is probably more common, they are taken up by phagocytic cells and carried into the peribronchial tissue, where they produce the tuberculous lesion, and the infection may then spread by lymphatics to the bronchial lymph-nodes. It is also claimed that bacilli which enter by the alimentary tract and pass through its wall, may, after reaching the mesenteric lymph-nodes, extend by way of the retroperitoneal and mediastinal nodes surrounding the aorta to the bronchial nodes and thence to the lungs. This, however, cannot be regarded as the common method.

Spread of the Process in the Lung itself :—

The structures in the lungs which are especially affected, and the character of the lesion, will depend largely on the special channel of invasion, as will also, to a large extent, the nature and method of spread of the process after it has started.

The chief methods of spread are :—

1. By the blood-stream.
2. By the lymphatics.
3. By the air-passages.
4. Local spread by infiltration.

Several of these methods of spread are frequently seen in the same case.

(A.) TUBERCULOSIS WITHOUT CAVITY-FORMATION

I. ACUTE TUBERCULOSIS

Acute Miliary[1] Tuberculosis. Though this variety of the tuberculous lesion may be confined to the lungs, it is more commonly part of a general infection, and due to the entrance of the bacilli into the blood-stream. The mechanism and site of entrance are not always obvious, but are in most cases due to the erosion, into a vein, artery or the thoracic duct, of a tuberculous nodule situated either in the wall of the vessel or in its immediate neighbourhood. In some cases, the bacilli may be conveyed directly to the thoracic duct by lymphatics. The bronchial, the mesenteric or the retroperitoneal lymph-nodes may show tuberculous infection, with definite caseation, and these lymph-nodes may then become the foci from which infection reaches the lung. For acute miliary spread to the meninges, *see* pp. 62 and 992.

Embolic Tubercle. In tuberculosis it is not uncommon to find local foci of infection in various organs, which can be explained only by the carriage of bacilli by the blood and their lodgment in these situations. The bacilli constitute the emboli. These local nodules are found in the kidney and brain; and the lung may become infected in a similar manner. Such foci may occur in the lung-tissue, become caseous and be the starting-point of a miliary tuberculosis, a bronchopneumonia with cavity-formation or chronic fibroid tuberculosis. The actual presence and therefore the distribution of bacilli by the blood is proved by the occasional cultivation of the organism from the blood.

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[1] *See* footnote on p. 1038.

Naked-eye Appearance. Large numbers of minute greyish nodules are seen scattered throughout the connective-tissue framework of the lung. They are irregularly rounded, often somewhat yellowish in the centre, and firm to the touch. They are also seen immediately under the pleura, and are distinctly raised above the pleural surface.

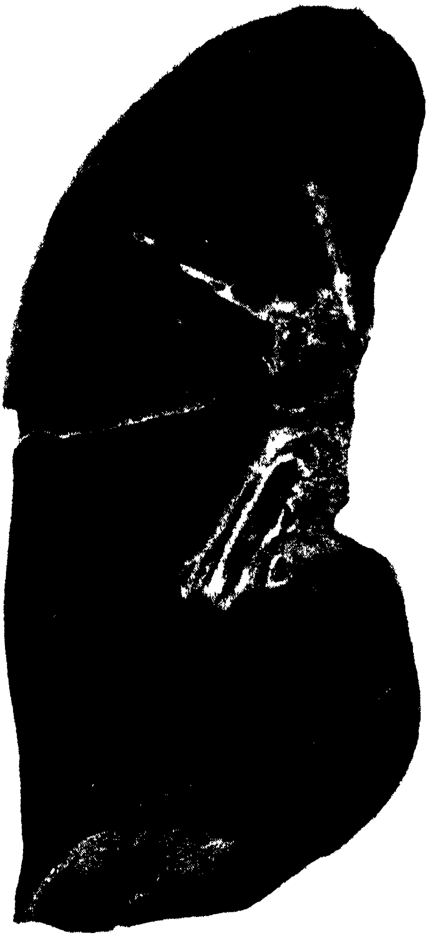

FIG. 332. *Lung,* Acute miliary tuberculosis. Note the small tubercles scattered throughout the whole lung.

Microscopically, in their early stages, these nodules are composed largely of lymphoid cells. In the connective-tissue framework there may be proliferation of connective-tissue and other cells to a slight degree, and little evidence of central caseation. Usually, giant-cells are not numerous. The walls of the alveoli may be thickened and these and the smaller bronchi invaded by the tuberculous process. In this way, collapse and local catarrh are produced.

Lymphatic Spread. In this form of spread, the bacilli are carried especially by the peribronchial lymphatics, and give rise to groups of small greyish nodules, often with an accumulation of carbon-pigment at the periphery, chiefly in the peribronchial connective-tissue. The nodules are usually firm to the touch, may show caseation and a varying degree of fibrosis, and are arranged in a racemose or " staphyloid " manner corresponding to the distribution of the branches of the bronchioles. A similar arrangement in little staphyloid clusters may be seen in bronchopneumonic tuberculosis, especially in the early stages where the main lesion is in the bronchioles. In such cases, the actual position of the tuberculous nodules can be determined only by microscopical examination.

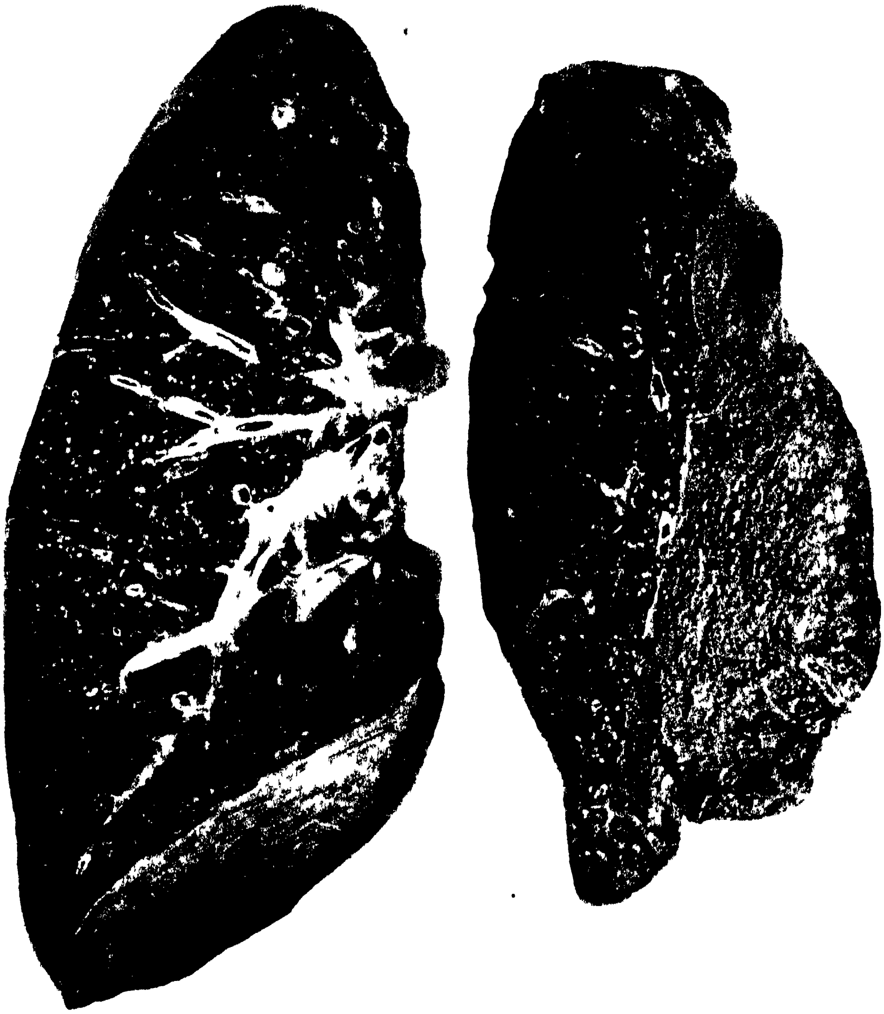

FIG. 333. *Lung.* Acute miliary tuberculosis. Note tubercles on the pleural surface of right-hand specimen.

The peribronchial lymphatic infection usually progresses slowly and tends to be of chronic type. Its characters are described under Chronic Tuberculosis, pp. 560, *et seq.*

FIG. 334. *Lung.* Subacute tuberculosis with some fibrous overgrowth towards upper part of lobe, and showing acute peribronchial spread into the lower lobe.

Air-Passage Spread :—

This form of spread gives rise to the catarrhal or bronchopneumonic form of tuberculosis. It is a frequent mode of secondary acute infection in the course of the more chronic cases.

Methods of Infection. The air-passages, especially the bronchioles, may become infected by the inhalation of extraneous dust or other particles con-

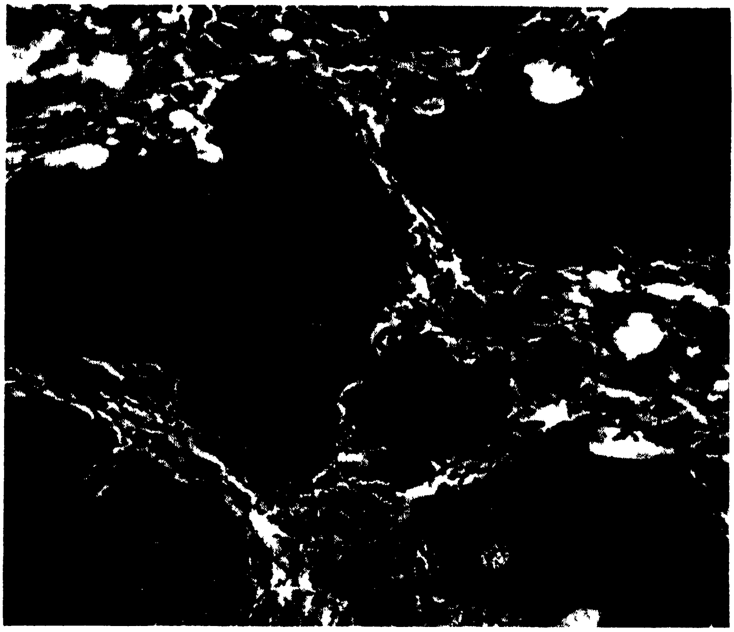

FIG. 335. *Lung.* Acute tuberculous bronchopneumonia, showing exudate in the alveoli and central caseation. × 25.

taining tubercle bacilli, or of secretions, caseous exudates or blood from tuberculous foci in the air-passages or the lung itself. An infection of this nature may arise by the erosion into the alveoli or into the bronchi of a tuberculous

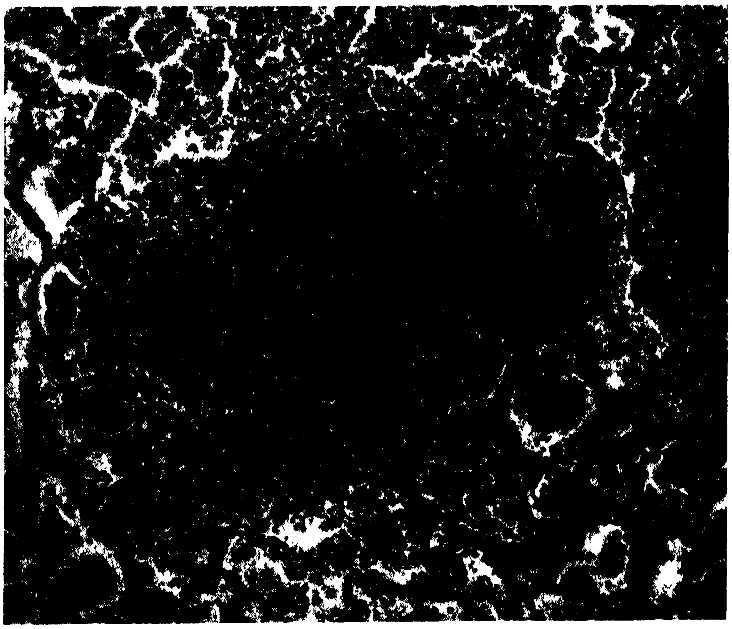

FIG. 336. *Lung.* Acute tuberculous bronchopneumonia. Note the consolidated and caseous central exudate, with obliteration of alveolar walls and alveoli. At the periphery, the extension is shown by the accumulation of the exudate in the unobliterated alveoli. × 100.

focus situated either in the peribronchial tissues or in the bronchial lymph-nodes.

Characters of the Lesions. The infective material produces in the minute bronchioles an intense catarrh, which spreads into the air-cavities. This catarrh is associated with rapid necrosis and caseation, not only of the inflammatory products, but also of the walls of the small bronchioles, the alveolar passages, and the air-cells. It may affect a part, or the whole, of one lobule, or a group of lobules, according to the size of the bronchiole primarily involved. The walls of the air-spaces become infiltrated with cells of lymphoid type, giving rise to compression and to obliteration of the alveolar capillaries. Giant-cells are usually scanty or absent, or may be found only in the peribronchial tissue in the original tuberculous focus. The intervening lung-tissue may be intensely congested, and œdematous, or may show hæmorrhage, catarrh, or the occurrence of a fibrinous exudate in the air-spaces—a condition resembling acute lobar or lobular pneumonia.

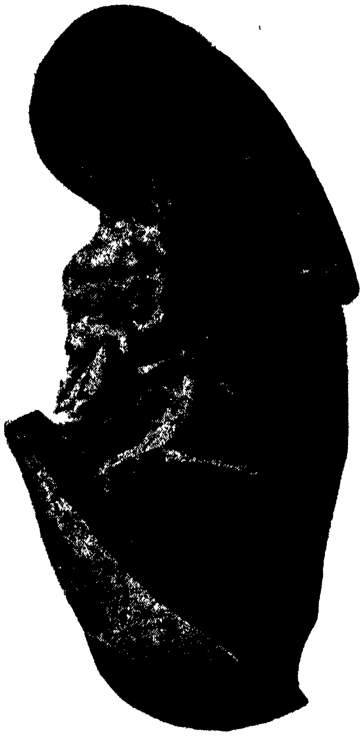

FIG. 337. *Lung.* Acute tuberculous bronchopneumonia, showing irregular pale caseous areas, in the centre of some of which the openings of the minute bronchioles can be seen.

Naked-eye Appearances :—

If the lobular bronchioles only are affected, minute white or yellowish nodules are seen, scattered irregularly on the cut surface, from which they may project slightly. They may be soft, and sometimes the outline of the bronchiole may still be visible in them. If the larger bronchioles are involved, the nodules become arranged in groups of from about 2 to 5 mm. in diameter (lower part of Fig. 338). These are yellowish in colour, and slightly raised above the surface of the lung. By confluence, larger areas are produced, and the lung presents a mottled appearance, the yellowish tuberculous areas tend to break down and produce acute cavities. The interlobular septa are swollen, and there may be œdema, and fibrinous, or catarrhal, pneumonia in the intervening lung-tissue.

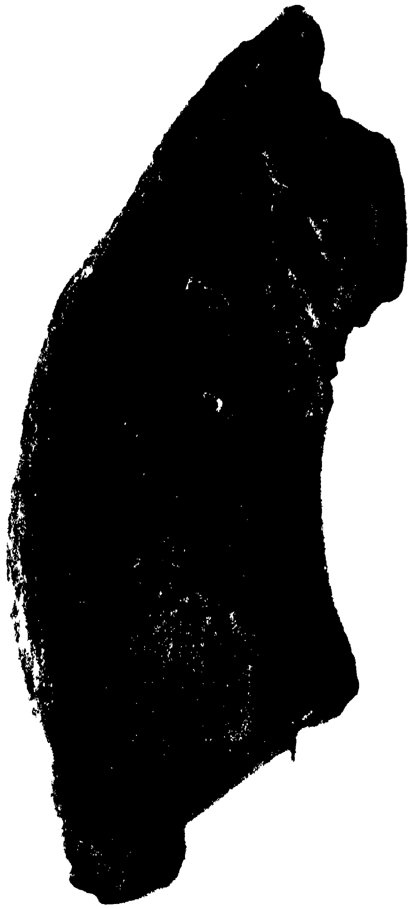

Fig. 338. *Lung.* Showing very advanced acute caseating tuberculous bronchopneumonia in a child's lung, with great thickening of the pleura.

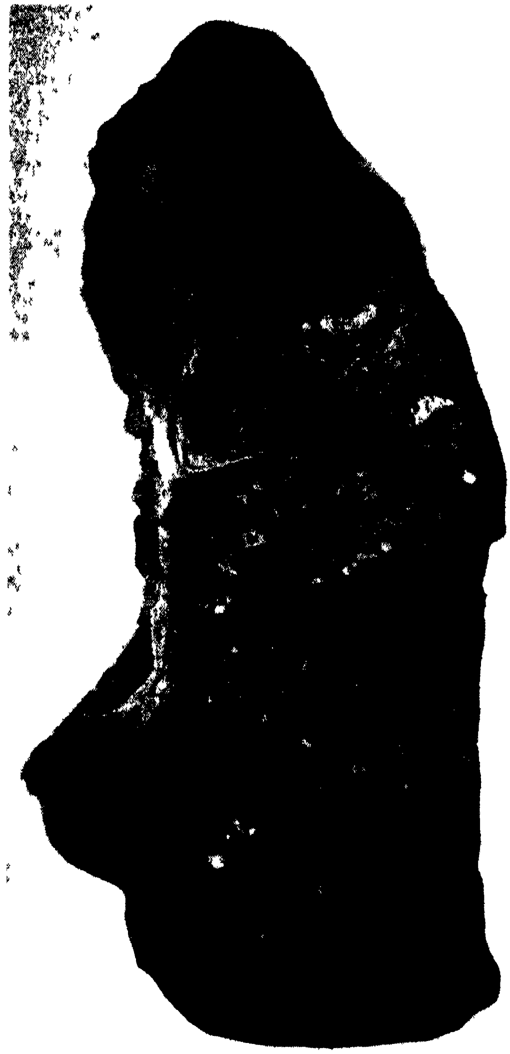

Fig. 339. *Lung.* Tuberculosis, showing chronic fibrosis and cavity formation in the upper lobe and more acute bronchopneumonic spread in the lower part of the upper and upper part of the lower lobes.

II. CHRONIC TUBERCULOSIS

In this form, the spread is by way of the peribronchial lymphatics, and directly from these into the lung-tissue. The earlier lesions are usually at the apex of the lung, and nodules or tubercles occur in groups in relation to the bronchi (Fig. 340).

Naked-eye Appearances. Such chronic nodules are characterised especially by: a homogeneous glistening appearance in their earlier stage, before the fibrous tissue becomes very dense: pigmentation, which is due partly to previous accumulation of carbon-pigment at the site of the original peribronchial lymphatics, and also to the increase of pigment which is associated with all chronic irritative conditions: fibrous overgrowth round the nodule, forming an indefinite capsule, either localised or extending into the surrounding lung-tissue, and producing extensive interstitial pneumonia. The centre of the area may show caseation.

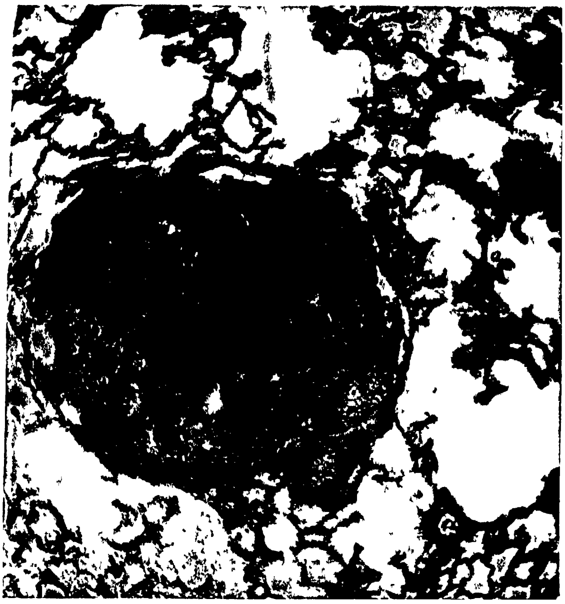

FIG. 340. *Lung.* A nodule in a progressive case of chronic tuberculosis, showing central caseation, giant-cell formation, and peripheral fibrous-tissue overgrowth. × 50.

Microscopically, the nodules are composed of fibrous or fibro-cellular tissue, with some caseation in the centre, and generally with giant-cell systems at the periphery (Fig. 340). The elastic tissue of the lung is absent from the nodules, and there may be little or no catarrhal reaction in the adjacent air-vesicles. Invasion of the wall of a bronchus is not uncommon, and in this way the bronchus may be completely blocked and an acute tuberculous bronchitis, and, subsequently, an acute tuberculous bronchopneumonia, may develop. Or again, the nodules may undergo healing, *i.e.*, become surrounded and shut in by a dense fibrous capsule (Fig. 341), the central part usually showing caseation and sometimes calcification; or the original focus may simply be represented by a dense pigmented and contracted fibrous scar.

Fibroid "Healed" Tubercle :—

In all tuberculous lesions, a varying ratio between the processes of destruction produced by the toxins of the bacilli and the processes of reaction against these on the part of the body-tissues can be observed. When the latter are successful in localising, or even in entirely neutralising, the effects of the former, they do so to a large extent by proliferation of the connective-tissue elements, which come to surround the diseased area and form a capsule which encloses and cuts it off from, and prevents its further spread into, the neighbouring tissues. These proliferative changes are found especially where the tuberculous process has been arrested, or where its development has been slow ; but they may also develop even in the more acute lesions. Thus, the minute tubercle-granulations of acute tuberculosis, especially the form which is spread by way of the lymphatics, may shrink, become fibrous, and leave only small scars of pigmented fibrous tissue ; or the nodules of bronchopneumonic tuberculosis may become surrounded by a zone of fibrous tissue, and the caseous contents of the nodule become dried up, inspissated and perhaps eventually calcified. The fibrous overgrowth is especially pronounced in the more chronic peribronchial form. The bronchus, the lumen of which is often completely obliterated, and the areas of lung-tissue which are associated with it and which may show caseation and calcification, are often surrounded by a zone of dense fibrous tissue. At the periphery of this nodule, a gradual extension of the fibrosis into the lung-tissue takes place and, in the later stages, may bring about the complete isolation of the tuberculous foci by the formation of a dense fibrous capsule around them. Its tuberculous nature may be detected histologically perhaps only by the presence of a few giant-cells.

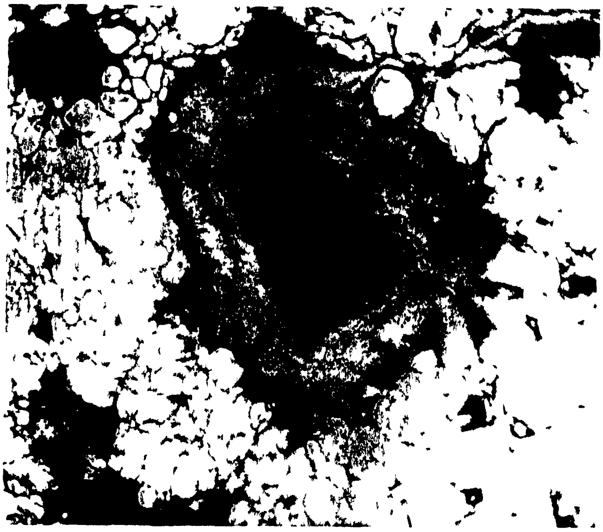

FIG. 341. *Lung.* Fibroid "healed" tubercle. Note the dense fibrous tissue zone around the central caseous area. × 10.

(B.) TUBERCULOSIS WITH CAVITY-FORMATION (PHTHISIS)

The term " phthisis " was originally applied *clinically* to the general wasting of a patient suffering from certain forms of tuberculosis ; and from this it has come to be applied also to the pathological condition of the lung, in which the tuberculous lesion leads to wasting of the lung-tissue with cavity-formation. The pathological processes which are concerned in the production of pulmonary phthisis are essentially the same as those already described under Acute and Chronic Tuberculosis, though there is usually a more progressive extension of the lesion, combined with greater consolidation of lung-tissue, and always a breaking-down and excavation of the caseous tuberculous material, *i.e.*, the formation of cavities.

The two essential processes in phthisis are **consolidation** and **cavitation.** Occasionally one lung only is affected, but, frequently, both are infected from the same source, either simultaneously or at different periods. The degree of spread is usually greater in one lung than in the other, and the characters of the lesions, even in the same lung, often show that there have been successive infections : or the intermittent and variable progress and spread of the same infection. The second lung may be infected, either by way of the bronchial lymph-nodes and lymphatics, or by inhalation into its bronchus of infected sputum which is being expectorated from the diseased lung.

Clinically, the disease is usually detected first at the apex, but some authorities maintain that the initial focus in the lung itself may occur at the outer part of the upper lobe or at, or near, the root. There is, however, a general agreement that from this focus direct local infiltration of the lung takes place, and, during the extension, infective material may reach the blood-vessels or bronchi and be carried to distant parts of the lung, and there produce a miliary or a bronchopneumonic tuberculosis. Thus a hemi-section of the lung may show a chronic phthisical cavity at the apex of the upper lobe and a miliary or a bronchopneumonic tuberculosis in the lower lobe (Figs. 339 and 343 to 345).

The process may extend also along the peribronchial lymphatics, until it comes to involve the smallest bronchioles, from which it spreads to the air-vesicles, forming little staphyloid or cluster-like nodules, often showing increase of pigmentation, and giving a mottled granite-like appearance to the section. Overgrowth of fibrous tissue tends to occur around .the nodules. Such gradual and progressive fibrous overgrowth is due especially to slow spread along the peribronchial lymphatics. The consolidation extends towards the surface of the lung and gives rise to repeated attacks of pleurisy, which lead to adhesions, and often to considerable fibrous thickening of the pleura over the consolidated areas.

The pathological appearances which are classified under the term "phthisis" present many variations. These are due partly to the rate at which lesions are produced, partly to the preponderance of one or other type of initial lesion, and partly to the intercurrence of inflammatory, degenerative or proliferative processes. Thus, the lesions which progress slowly show a greater degree of fibrous overgrowth, pigmentation and calcification, than do those which develop rapidly. Where a bronchopneumonic form predominates, there is likely to be cavity-formation of a more irregular type than when the prevailing method of spread is by lymphatics; and again, a phthisis of slow development may, at any period in its course, assume acute characters and advance rapidly. In addition, there may be changes in the type of the lesion. Thus, a chronic tuberculous peribronchitis may, by the erosion of the nodule into the bronchus, become an acute tuberculous bronchopneumonia, or, by ulceration into a vessel, give rise to the acute miliary form of the disease. The two lungs may show lesions differing in type.

Thus it will be seen that, from the consideration of the pathological anatomy or histology of phthisis, it is, in many cases, extremely difficult, or even impossible, to draw a definite line of demarcation between the acute and the chronic forms. It is, however, convenient, for descriptive purposes, to classify the condition into cases which are acute and those which are chronic; but it must always be remembered that this distinction is one merely of degree and is therefore more or less artificial, and that varying admixtures and combinations of both acute and chronic processes co-exist in individual cases.

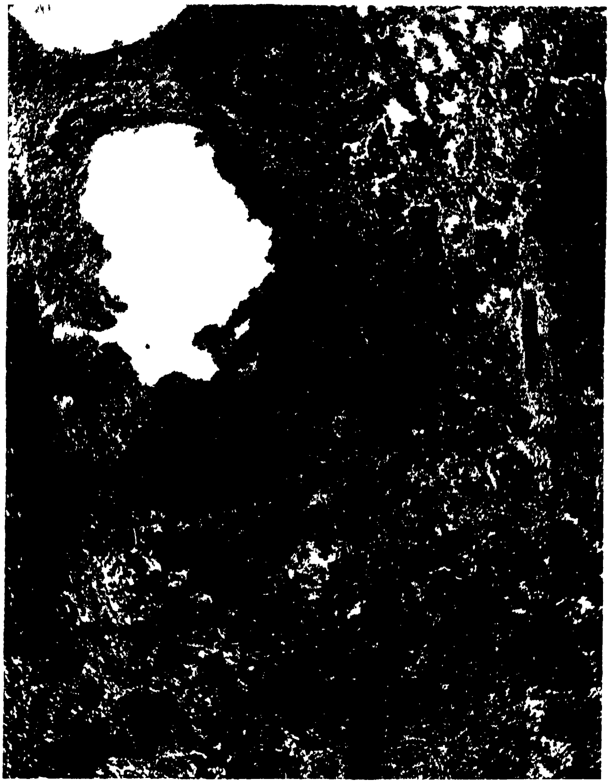

FIG. 342. *Lung.* Acute phthisis, showing a small cavity with irregular and ragged caseous wall, and also consolidation throughout the remainder of the lung-tissue. × 35.

I. ACUTE PHTHISIS

Under this term we include only the more rapidly progressing forms of tuberculosis, in which the fundamental lesion is consolidation by a tuberculous bronchopneumonia with necrosis and caseation, followed by cavity-formation. The consolidated areas may occur as minute scattered foci, as larger lobular areas, or as patches occupying considerable portions of the lung—these larger areas being formed by the confluence of smaller patches. The intervening lung-tissue always shows a varying degree of congestion and œdema, and very often acute fibrinous or catarrhal pneumonia. When the tubercles reach the surface of the lung, patches of pleurisy develop over them. In a certain proportion, the caseous nodule is surrounded by a fibro-cellular zone, in which giant-cells are present. This proliferation of fibrous tissue, and the presence of giant-cells, indicate chronicity. The cavities may be rapidly formed and numerous. They are often small and have ragged caseous walls, and may be produced by the softening and breaking down of caseous bronchopneumonic areas or—and probably more frequently—by ulceration and dilatation of the small bronchi (Fig. 343). In our experience, cavity-formation is comparatively uncommon in young children.

Sometimes, the acute destructive changes and softening may be more extensive and come to involve considerable portions of lung-tissue, producing large cavities, from which the caseated and necrotic tissue may reach the bronchi and be expectorated. The sputum contains fragments of elastic tissue and other elements of the fibrous-tissue framework of the lung, as well as, in some cases, enormous numbers of tubercle bacilli.

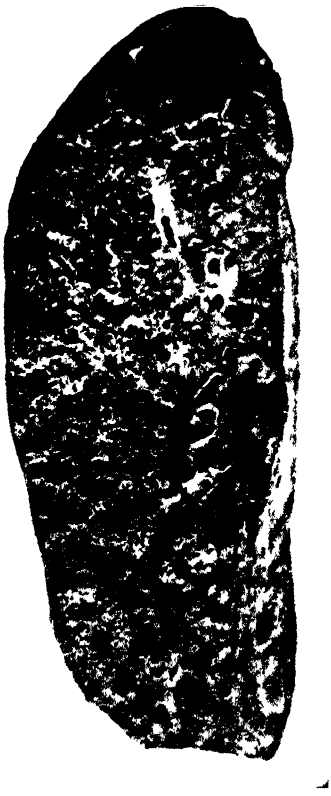

Fig. 343. *Lung.* Acute phthisis, showing a larger, somewhat chronic cavity at the apex, and also numerous smaller, irregular, acutely-formed cavities in the remainder of the lung-tissue. Many of these cavities are obviously dilated bronchi with ulcerated walls.

II. CHRONIC PHTHISIS :—

The essential lesion in this form of the disease is consolidation brought about by the development of peribronchial tubercles. There may, in addition, be nodules in the fibrous tissue of the septa, and in the deeper layer of the pleura. Around and from these peribronchial foci, proliferation of fibrous tissue takes place and extends into the lung-tissue, producing the condition of chronic tuberculous interstitial pneumonia, which may become extensive, and may be the most obvious lesion. In and between the layers of fibrous tissue, whitish or yellowish-white caseous tuberculous nodules may be present, giving rise to so-called **fibro-caseous tuberculosis.**

Cavities are formed by the caseation and softening of the peribronchial nodules and their erosion into the bronchus, into which the softened material passes and is then expectorated. Perhaps, more commonly, the cavities are bronchiectatic in origin. The walls of the bronchus, into which the peribronchial nodule has discharged its contents, become attacked and softened by the spread of the tuberculous process. The bronchi, in this way, are less resistant to the inspiratory efforts, and a gradual, and usually irregular, dilatation takes place, aided, no doubt, by the external traction of the proliferated and contracting fibrous tissue surrounding the affected bronchus. The walls of the bronchi may become completely destroyed, and the wall of the cavity may consist of the proliferated fibrous tissue of the lung—for example, the thickened interlobular septa, or even the newly formed bands of fibrous tissue which are produced by the interstitial pneumonia and which bring about the consolidation in that condition.

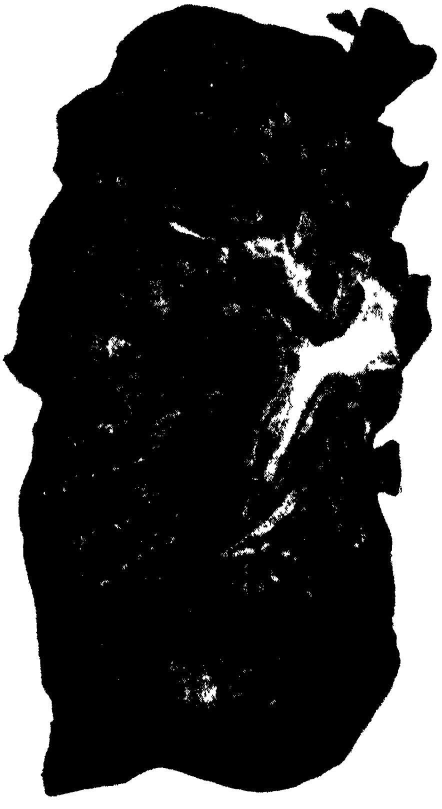

FIG. 344. *Lung.* Chronic phthisis, showing numerous cavities with fibrous walls and caseous contents. Note in the cavity near the apex the exposed branching arteries, and in the lower lobe a bronchopneumonic spread.

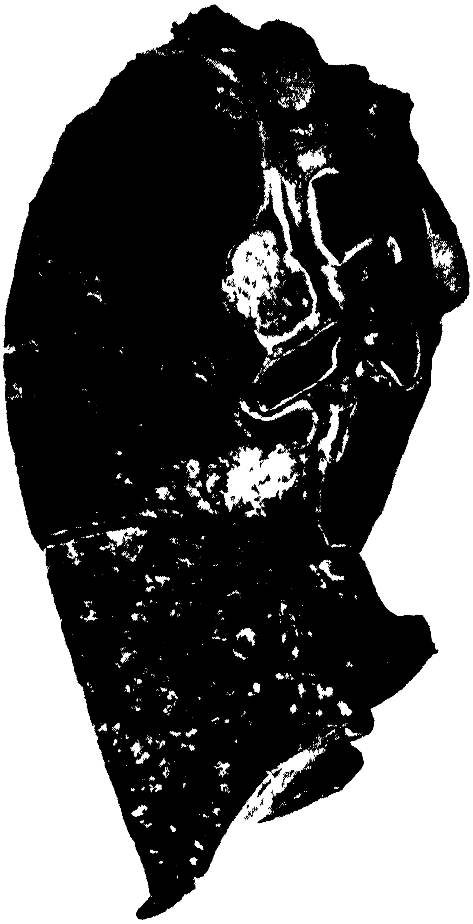

FIG. 345. *Lung.* Chronic phthisis, showing a large irregular cavity in the upper lobe. In the lower lobe there are scattered acute nodules grouped in clusters around the small bronchi, and also several small, more acute cavities. The bronchial lymph-nodes are enlarged and caseous.

Character of the Larger Cavities. The chronic cavities are often very irregular in outline, and sometimes sinuous or multilocular. They vary much in size, are found usually near the apex, and sometimes a single cavity occupies the greater part or even the whole of the upper lobe. More commonly, however, smaller cavities are also present, especially in the upper part of the lower lobe. The lining-membrane is smooth and fibrous in the long-standing chronic forms, or coated with caseous material in the less chronic types. The walls of the cavities are often very vascular. Crossing the cavities, or projecting from their walls, there are generally bands of fibrous tissue corresponding with the more resistant interlobular septa and peribronchial connective tissue, and sometimes containing partially obliterated bronchi and vessels. These vessels may become varicose, and, on account of the loss of support, small aneurysms tend to form on them, and, if these rupture or become eroded, serious hæmorrhage is likely to occur unless, as frequently happens, thrombosis with organisation of the thrombus has occurred in the vessels. The cavities, however formed, tend to increase in size, not only by progressive erosion of their walls and distension by long-continued coughing, but by being dragged upon externally by the contracting fibrous tissue of the increasing chronic interstitial pneumonia. The contents of the cavities, consisting of caseous and necrotic tissues and exudate, may undergo decomposition owing to the entrance of putrefactive bacteria ; or, if pyogenic bacteria gain entrance, they give rise to local suppuration, or to septicæmia or pyæmia. The infective contents of the cavities, entering the larger bronchi and trachea,

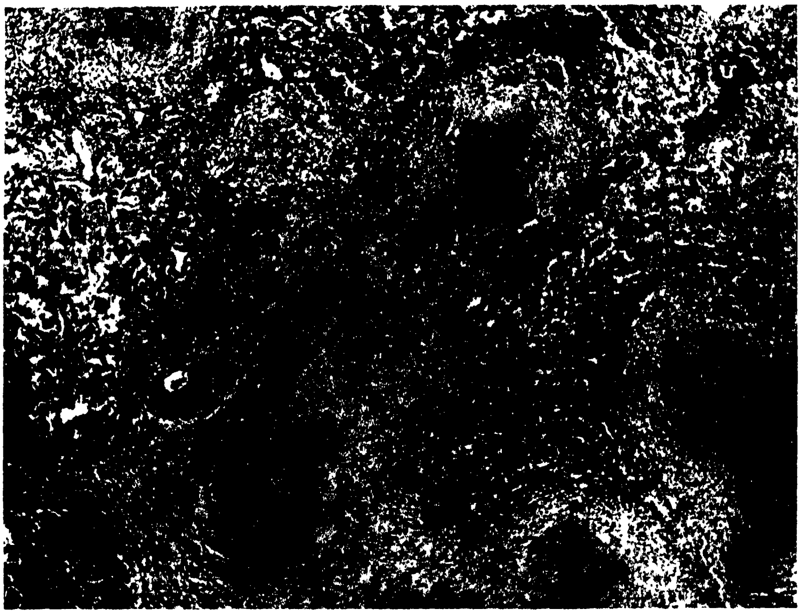

FIG. 346. *Chronic phthisis* This section is taken from a part in which cavity-formation is almost absent. It shows the irregular tuberculous nodules (with caseous centre, giant-cells, and fibro-cellular zone) which have fused to form dense consolidated areas. Note the "pseudo-glandular" character which the alveolar spaces have assumed. × 35.

lead to the production of ulcers in the walls of these structures, especially prominent between the rings of cartilage. Similar ulceration may occur also in the larynx. The pleura over the chronic cavities often becomes much thickened and adherent to the chest-wall, such thickening acting as a protection against perforation. Occasionally, however, perforation does occur—usually in the more acute cases—with resulting pyo-pneumothorax.

The microscopical characters of such chronic tuberculous nodules are similar to those already described (p. 560 *et seq.*) under Chronic Tuberculosis. A varying degree of consolidation, due mainly to overgrowth of fibrous tissue, occurs at places, often giving rise to dense masses of tissue in which groups of caseous tubercle-nodules are seen (Figs. 346–7).

The bronchial lymph-nodes may show foci of tuberculosis, with giant-cell systems, or caseation throughout. Calcification is common. In some instances, especially in cases of long-standing and associated with pyogenic infection, amyloid degeneration is demonstrable in them, and also in the liver, spleen and kidney.

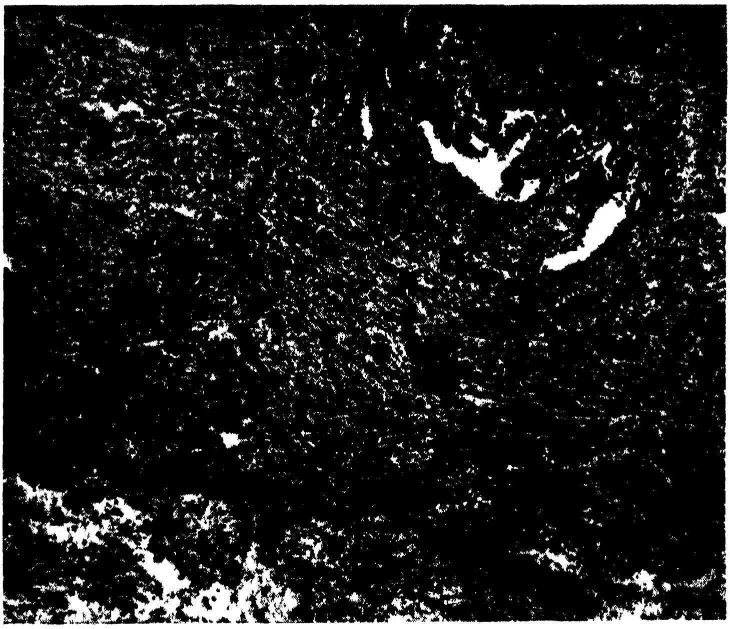

FIG. 347. *Lung.* Section of wall of cavity in chronic phthisis, showing fibrosis, the compressed alveoli on the right and the degenerated contents of the cavity along the lower margin of the illustration. × 50.

Hæmorrhage from Phthisical Lungs. Though tuberculous nodules are practically non-vascular, they give rise to an irritative or inflammatory reaction in the tissues in their immediate neighbourhood. The vessels thus formed may, in late and very chronic stages of the disease, become obliterated by thrombosis. It is from the non-obliterated vessels in these situations, *e.g.*, in the wall of a cavity external to the softened caseous lining, that hæmorrhage is likely to occur. It follows that hæmorrhage from such vessels is commoner in the acute or progressive cases of pulmonary phthisis.

Hæmorrhage may occur at various periods of the disease. In **early** cases it may be due to :—

(i) Softening and erosion of a peribronchial tuberculous nodule, forming a communication between a bronchus and a branch of the pulmonary artery (or possibly a tributary of the vein) or a bronchial vessel. This is probably one of the most frequent causes of early hæmoptysis.

(ii) Ulceration of the wall of a cavity eroding into a small vessel. As the effused blood often contains tubercle bacilli, and is inhaled into other bronchi, these hæmorrhages may give rise to an acute spread of the disease.

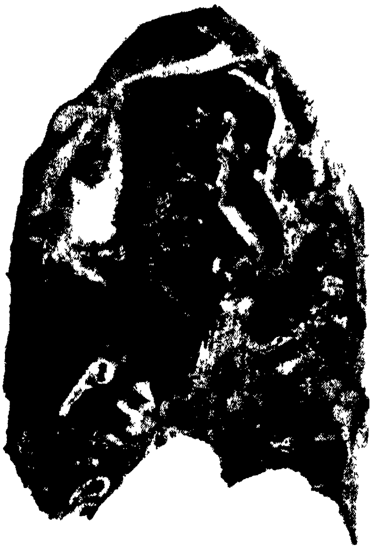

FIG. 348. *Portion of an Injected Lung.* Its divided surfaces show many non-vascular tubercles. The tissue has been destroyed by ulceration, which has led to the production of two considerable cavities ; the upper, with irregular and still ulcerating walls, is traversed by two branches of the pulmonary artery, still pervious.

Later, hæmorrhage may be due to :—

(i) Ulceration of the walls of a cavity eroding into blood-vessels.

(ii) Engorgement and rupture of capillaries in the vascular walls of cavities, giving rise to a condition of oozing from the walls.

(iii) Rupture of, or erosion into, small aneurysms on branches of the pulmonary artery. Such rupture, of even a minute aneurysm in the walls of a cavity or in some of the fibrous bands traversing it, will lead to a fatal hæmorrhage.

(iv) Ulceration into a tributary of the pulmonary veins is not common, but may occur.

(v) Rapid softening and breaking down of a large portion of lung-tissue will cause hæmorrhage by opening into the vessels. Except in extremely acute cases, such a result is infrequent, because the vessels round the tuberculous focus usually undergo obliteration—the tuberculous nodule itself being thus relatively non-vascular.

Syphilis of the lung is described on p. 87.

"Sarcoidosis" of Boeck. In this disease infection of the lung is common (pp. 77–8).

MYCOTIC INFECTIONS OF THE LUNGS

Moniliasis (pp. 93 and 704). The presence of the "thrush-fungus" (*Monilia albicans*) in sputum, independent of the nature of the primary pulmonary disease, is not uncommon. As mentioned on p. 93, the infection may spread to the bronchi, and, in a number of cases investigated clinically, **bronchial** and **pulmonary moniliasis** appears definitely to have been present. Although perhaps most often a secondary invader, for example, in patients suffering from tuberculosis, cases have been recorded in which *Monilia albicans* was thought to be the primary, or at all events the most important, infective agent, the resulting condition being classified clinically as mild, intermediate, or severe—the last of these not infrequently tending to simulate pulmonary tuberculosis.

Aspergillosis (pp. 94 and 503). *Aspergillus fumigatus* produces a chronic infection in the lungs, characterised by the presence of small grey nodules which undergo necrosis and cavitation, and are associated with areas of bronchopneumonia. Masses of the mycelium are found in the cavities and extend into the surrounding bronchioles and air-cells. In some cases, the fungus has been observed in the sputum during life.

Blastomycosis. Though the lesions in this disease (p. 93) are mostly in the skin, the infection may spread by the blood-stream to the lungs and elsewhere and produce nodules resembling those of tuberculosis. Cavitation is present, and is the result of suppuration rather than of necrosis. The presence of the yeast-like organisms can be detected in the sputum.

Streptothricosis (p. 550) :—

Actinomycosis. The organism of this infection (pp. 91 and 550)—*Actinomyces bovis* (or *Streptothrix actinomyces*)—may reach the lung by inhalation, or by extension from an actinomycotic abscess in some part of the alimentary tract, including the mouth. The lesions are suppurative—producing multiple abscesses which burrow in the lung-tissue and extend to the chest-wall and spine, forming numerous sinuses : but usually not involving the bronchial lymph-nodes. The fungus is seen in the pus and in the sputum in the form of " sulphur-granules," so called because of their yellowish colour—these being composed of masses of the branching mycelium.

Other forms of streptothrix-infection are rare in man. *Actinomyces* (or *Streptothrix*) *asteroides* of Eppinger (pp. 92 and 550) produces minute greyish areas, resembling miliary tubercles, scattered throughout the lungs. These areas are small suppurative foci in which the branching filaments of the fungus are present. Secondary lesions in the brain and elsewhere may develop.

SECTION V

TUMOURS OF THE AIR-PASSAGES AND LUNGS

Simple tumours such as papillomas, sometimes multiple, of the vocal folds are not uncommon, and an increased liability to their occurrence in the larynx of men gassed in war has been noted. Soft and hard " fibromas " of the vocal folds are fairly common ; but many of the lesions so described,

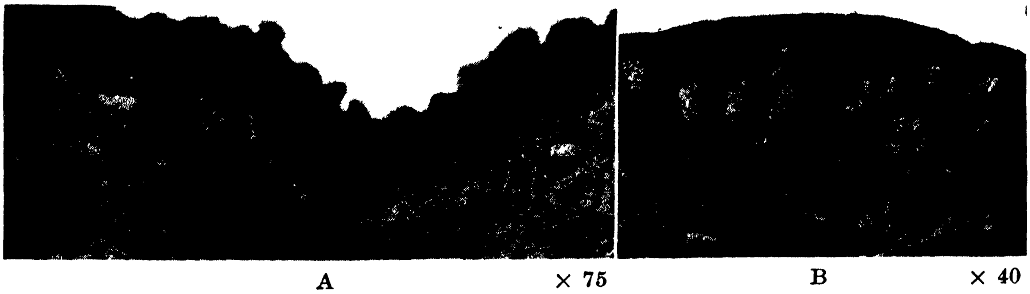

FIG. 348X. *Leukoplakia of the vocal folds* (biopsy-specimens).

A. Low-power view of section of a patch of squamous epithelial thickening with slight " keratosis " (cause unknown—W. R. " negative ") in a man aged 58. There is no ulceration of the surface or any cellular infiltration of the submucous tissues.

B. Similar section of a patch of thickening, in a man of 57, with history of syphilitic infection eighteen years previously, with gumma of the tongue (treated with arsenicals, and W.R. now reported " negative "). Note epithelial proliferation and subjacent chronic granuloma-like changes. Van Gieson and hæmatoxylin.

especially laryngeal "polypi," are in reality non-neoplastic in nature and origin (*cf.* p. 504). These, and the closely allied "vocal nodules," are found especially on the vocal folds of persons who habitually over-strain

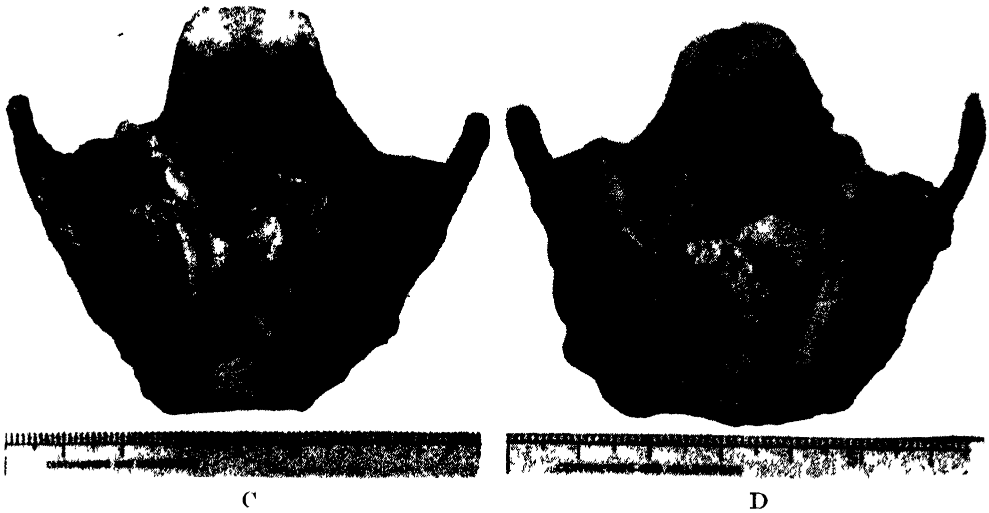

FIG 348Y. *Squamous epithelioma of larynx* (operation-specimens).
C. From a man aged 33, showing irregular, projecting and ulcerating malignant tumour affecting both vocal folds (For character of the tumour-cells, *see* Fig F, below)
D. From a woman, aged 63, showing malignant tumour of right vocal fold. (Fig. E, below).

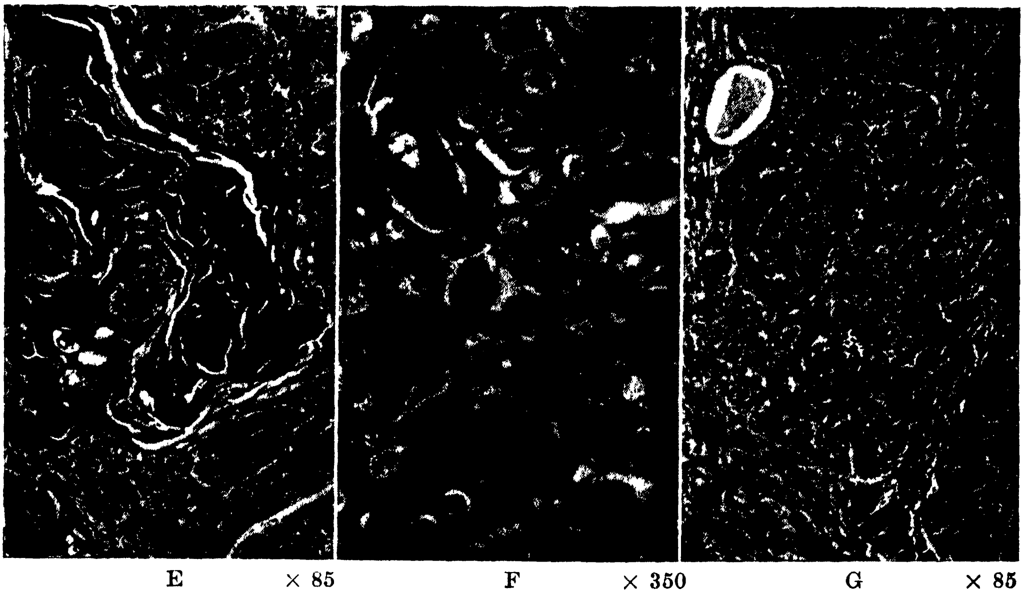

FIG. 348Z. *Malignant laryngeal tumours.*
E. *Squamous epithelioma* (Fig. D, above): a grade-I tumour showing pronounced differentiation, with large areas of cornification.
F. *Squamous epithelioma* (Fig. C, above): a grade-III tumour, showing pronounced anaplasia of the cells, although some still retain their "intercellular bridges."
G. *Adenocarcinoma* arising as "subglottic tumour" *from mucous glands* of laryngeal mucous membrane below level of right vocal fold, in man of 74. Van Gieson and hæmatoxylin.
(All of these specimens in Figs. 348X, Y and Z, are by courtesy of Mr. Lionel Colledge.)

the voice. The repeated irritation produces congestion and œdema of the loose subepithelial tissue of the folds, followed, perhaps, by thrombosis of the thin-walled veins and hyalination of the affected submucous tissue. Lipomas, myomas and lymphoid tumours are uncommon : and chondromas very rare ; but osteomas and osteo-chondromas of the larynx, and also of the trachea and bronchi, occasionally occur. Simple adenomas of the bronchi are mentioned on p. 576. Primary sarcomas and endotheliomas are said to occur, but, in this connection it should be kept in mind that primitive or actively malignant carcinomas (*see under* " oat-celled carcinoma " of bronchi, p. 571) may come to resemble and be mistaken for malignant mesoblastic tumours. The commonest and most important primary malignant tumours of the air-passages are carcinomas of the larynx and of the bronchi.

Carcinomas of the Larynx. A considerable variety of lesions of the larynx, especially of the vocal folds, may simulate " cancer " clinically, or may themselves undergo malignant metaplasia—for example, chronic inflammatory thickenings, either nodular or diffuse (p. 504) : keratoses or leukoplakias of syphilitic or of unknown ætiology (Fig. 348x, A and B) : chronic inflammatory lesions which have become polypoidal : as well as papillomatous and fibromatous tumours, originally simple. The commonest site of all these lesions is the vocal fold itself and the intermediate region of the anterior commissure. StClair Thomson [1] classifies carcinomas of the larynx into four groups :—

(A) **Intrinsic carcinomas of the larynx,** originating almost exclusively from the vocal fold itself, especially in the region where the ciliated epithelium lining the laryngeal sinus undergoes transition into stratified squamous epithelium to cover the upper surface of the vocal fold : sometimes from the epithelium of the laryngeal sinus or its mucous glands, especially their ducts : or from the vestibular folds (ventricular bands or false cords).

(B) **Subglottic carcinomas,** arising from the mucous membrane of the larynx below the level of the vocal folds, especially over its anterior part, or over the inner (*i.e.* under) surfaces of the vocal folds themselves.

(C) **Extrinsic carcinomas,** including tumours arising from the mucous coverings of epiglottis, piriform fossæ, the arytenoids, and the posterior or pharyngeal surface of the cricoid cartilage (" post-cricoid cancer "), or from the ary-epiglottic folds.

(D) **Carcinomas of " mixed " or undetermined origin,** mostly in patients in whom, when first seen, the growth has already become so advanced as to involve both intrinsic and extrinsic structures.

Carcinoma of the larynx is rare below the age of 40, and commonest between the ages of 40 and 50. The intrinsic tumours are ten times commoner in males than in females ; whilst the posterior cricoid variety of extrinsic cancer is said to occur more frequently in women. Squamous epithelioma of the vocal folds is by far the commonest histological type (96 per cent.) of intrinsic carcinoma : a few, however, being basal-celled (p. 339) : and still fewer of papillary or of adenocarcinomatous types (1 per cent. each).

Bronchial Carcinomas (sometimes described as " bronchogenic" carcinomas). The macroscopic appearances of these tumours vary greatly. They may

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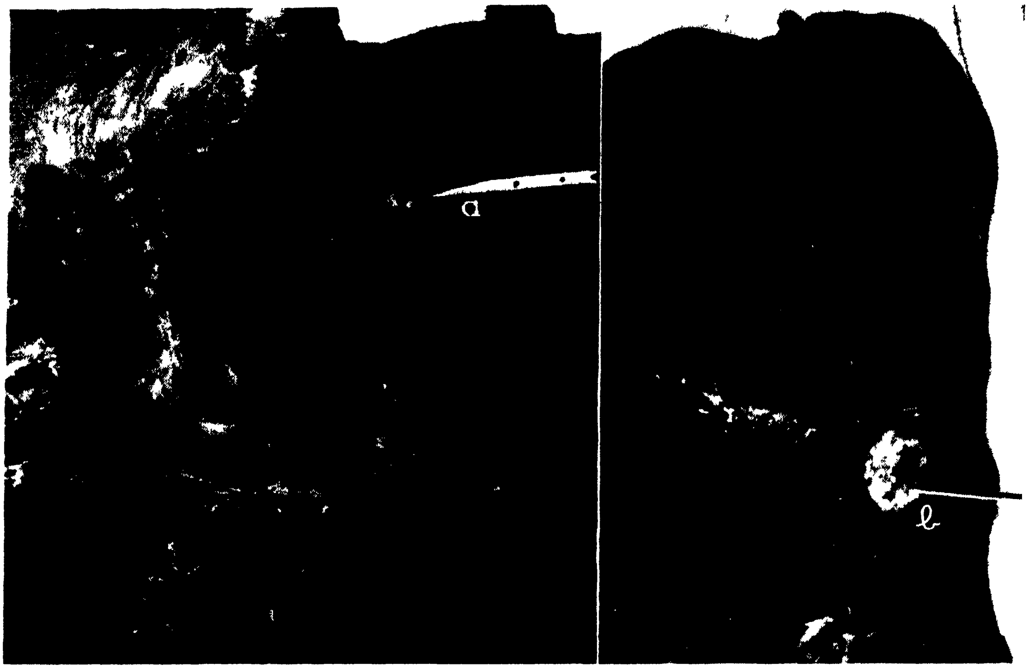
[1] *See* " Cancer of the Larynx," by StClair Thomson and Lionel Colledge, London, 1930, p. 13.

FIG. 349. *Lung.* Primary bronchial carcinoma.
(Series of cases to illustrate diversity in size and position.)

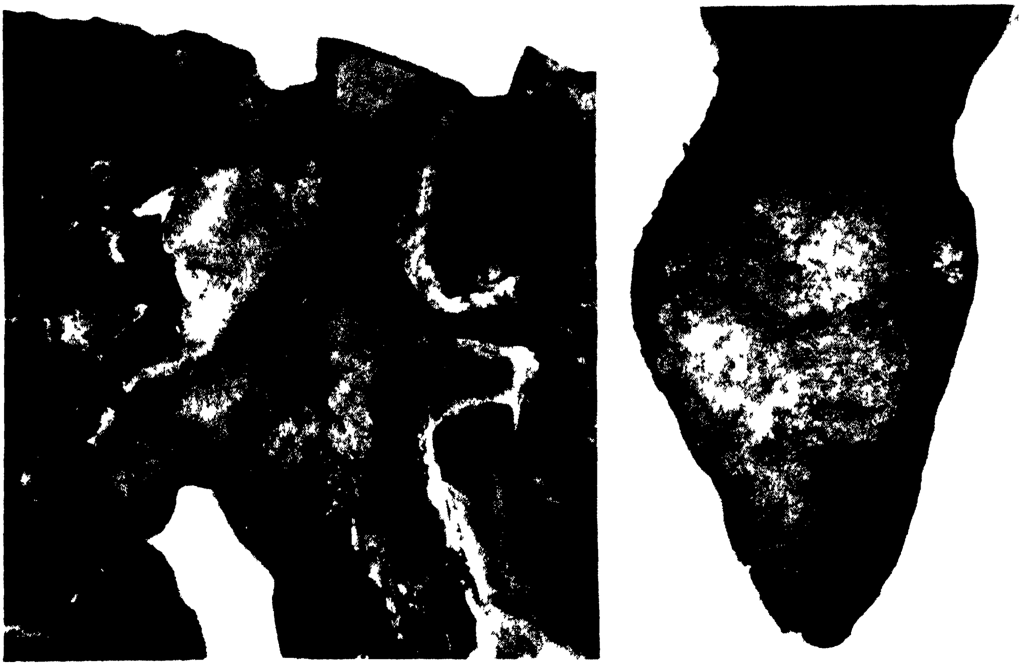


(A)

(A) Section through left upper lobe from man aged 47, to illustrate a minute bronchial tumour (*a*) which gave rise to extensive metastases in brain and elsewhere (Fig 725 (C), p 1147)
(W E H cases *See* footnote on p 574)

(B)

(B) Section through right upper lobe showing eparterial bronchus (*b*) blocked by a comparatively small primary tumour in a man of 55. (*See* Figs 351 and 733–4, p



(C)

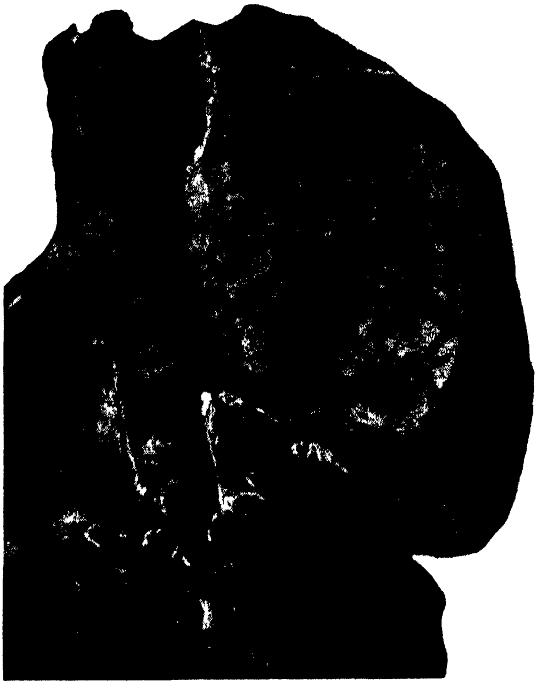
(C) A more extensive primary carcinoma attacking primary bronchus in a man aged 52 Secondary growths were found only in the suprarenal medulla on each side
. Norah Schuster.)

(D)

(D) Large primary lung-tumour occupying lower part of left upper lobe in a man aged 56. (*See* Figs 352 and 354 (B), also from this case.)

appear as whitish nodules at the root of the lung in relation to a main bronchus: or papillomatous masses projecting into the lumen of a bronchus: or merely as roughened patches on the bronchial mucous membrane. There is considerable variation in size, some forming large masses extending deeply into the lung-tissue, others being very small—perhaps 1 to 2 cm., or even less in diameter and requiring careful search for their detection (Fig. 349 (A)). A miliary form with minute nodules scattered throughout the lung is probably secondary to a primary bronchial carcinoma: or to a metastasis from it within the lung itself (p. 274): or it may be derived secondarily or indirectly from metastases in some other organ or tissue. A diffuse form, its naked-eye appearance simulating the grey-hepatisation stage of pneumonia, also occurs. Though the microscopical characters of individual tumours are highly pleomorphic, the tumours may for convenience of study be divided into three principal types.

1. The **anaplastic** or "**oat-celled**" form, in which the main mass of the growth consists of ovoid, oat-shaped or spindle-shaped cells arranged sometimes more or less parallel to one another, or in a rosette-fashion, or in groups having an alveolar arrangement. In these cells, the nuclei are relatively large and the cytoplasm scanty, simulating those of the cells of sarcomas. Other types of cells — cubical, columnar and squamous—are sometimes also present and are regarded as **transitional** cells, and neoplasms of this group really represent **variants** of the **adenocarcinomatous** and **squamous-celled types** described below, in which a higher level of cellular differentiation has been attained. Many of these tumours of anaplastic type were formerly believed to be sarcomas, and their recognition as belonging to the group of bronchial carcinomas is one of the factors which accounts for the apparently greatly increased incidence of primary malignant tumours of the lung. The majority, if not all, of these carcinomas originate from the bronchial mucous membrane—probably, in most instances, from the deeper layers of the epithelial lining, the cells of which resemble those of the tumour.



(E)

Fig. 349 (*continued*). (E) Large primary bronchial carcinoma occupying most of right upper lobe and invading mediastinum, trachea and œsophagus (the last not shown in the photograph), in a man of 68, a carpenter.

The starting-point of the growth is usually the mucous membrane of a bronchus at or near the root of the lung, but in other instances bronchi elsewhere may be primary sites. The tumours may, as already noted, be small and easily escape detection (Fig. 349 (A)), but usually they are large and soft, and give rise to early metastases. No single causal factor has so far been definitely established. The inhalation of dust from tarred roads and the waste-products from motor cars has been suggested as a possible cause, and much experimental work has been brought forward in support of this suggestion. Argyll Campbell (1934–43)[1] has shown that road-dust with a content of only 2 per cent. of tar is capable of raising the lung-tumour rate from 8 to 80 per cent. in mice subjected for long periods to the inhalation of an atmosphere containing it. Other observers have recorded an increased incidence of lung-tumours in mice as the result of repeated applications of tar to the skin. This experimental work, especially that of Campbell, is certainly highly suggestive, and it is not improbable that the inhalation of these tar-products and other irritating substances (including, perhaps, the products of the "dry-distillation" of tobacco) are important factors in the increased incidence of lung-tumours observed among the general population in recent years. The high incidence of cancer of the lung among the workers in the Schneeberg Mines in Bavaria suggests that certain irritant dusts (cobalt, nickel, iron, arsenic) might account for this, as miners in other parts of the world exposed to irritant dusts do not have this high incidence. In patients with silicosis, for example, the incidence of carcinoma of the lung is said not to be demonstrably higher than it is in the general population. There seems, therefore, to be some special factor in these mines, and it has been suggested that radio-active emanation may have some causal association. A similar development of cancer has been noted among the workers in the pitchblende (radium) mines in Joachimsthal in Bohemia—twenty miles from Schneeberg.

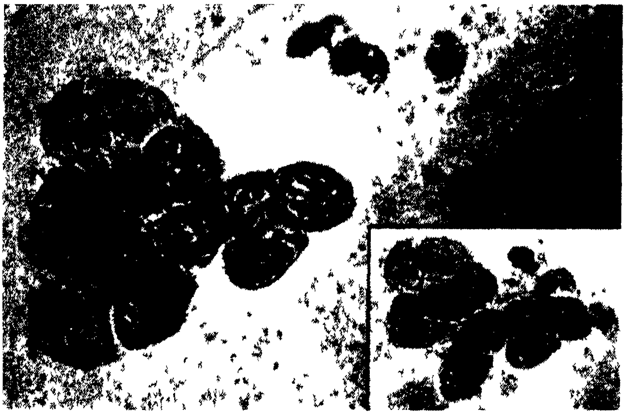


FIG. 350. *Bronchial Carcinoma.* A typical clump of "malignant cells" in the sputum from a case of "cancer of the lung" demonstrated by the toluidin-blue fresh-wet-film method. Note mitotic figures in the monaster and dyaster phases at the upper left part of the little mass of cells. Inset the same clump under ordinary high power (× 400). Toluidin-blue. × 1250. (W. E. H. case.)

NOTE. *The Diagnosis of Malignant Cells in Sputum by "Fresh-Wet-Film" Methods*, employed at the Royal Chest Hospital since 1914, was the subject of a demonstration and paper by the present writer (W. E. C. D.) on "The Cytology of the Sputum," at the Second Annual General Meeting of the British Pathologists' Association (now the Association of Clinical Pathologists), held at the Royal Free Hospital, London, *on January 26th*, 1929—the actual fresh-wet-film from which the above illustration was made being shown at that meeting

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[1] "Lung Tumours in Mice and Man," by J. Argyll Campbell, *Brit. Med. Jour.*, 1943, *i.*, 179.

2. **Adenocarcinoma,** in which the cells are mainly spheroidal or columnar in shape, but in which various transitional and aberrant forms are found, are fairly common. The cells may contain, and may also secrete, mucin—a phenomenon which has also been observed in their metastases in other organs. The cells of this type of tumour also take their origin from the epithelium of the bronchi and often exhibit a tendency to papillomatous growth.

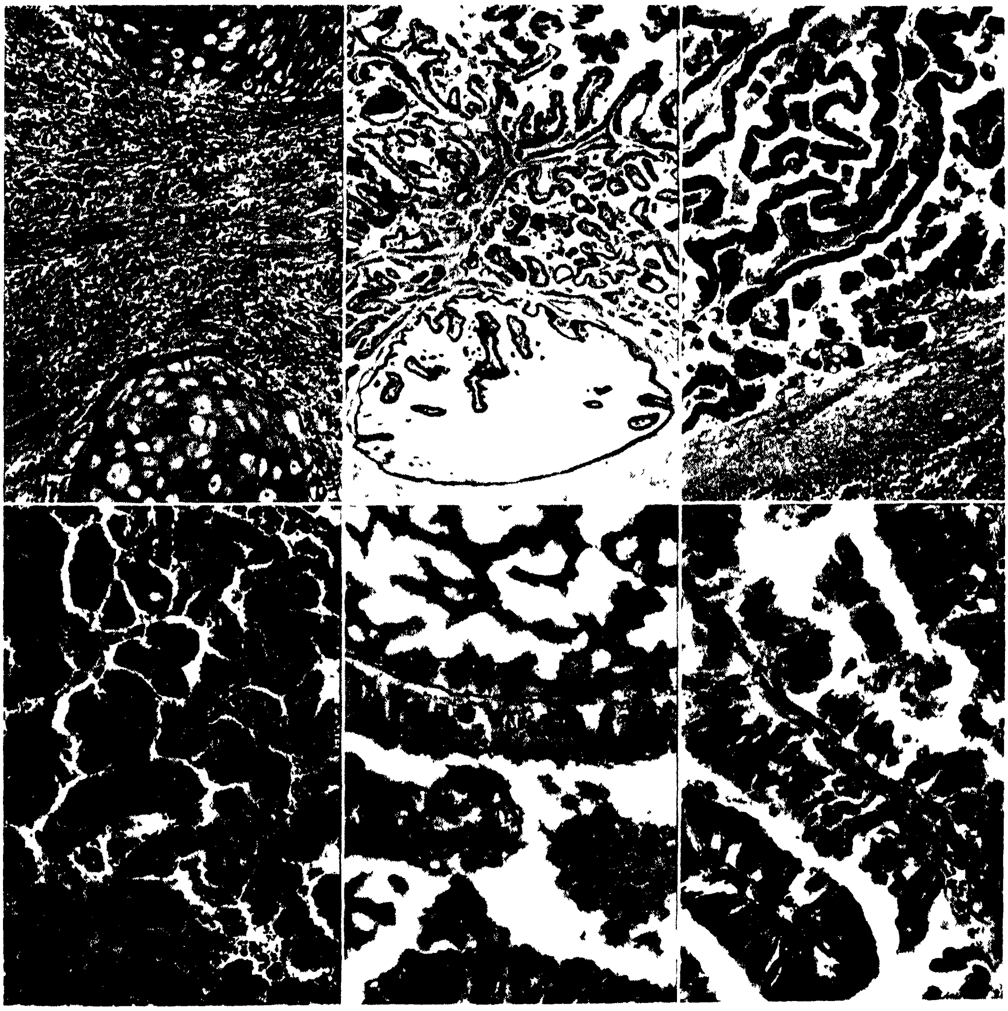
Fig. 351. *Bronchial carcinoma*: varied appearances in the primary growth and metastases in an individual case. (W. E. H. case (B) in Fig. 349, p. 570.)

(*a*) Primary growth in wall of eparterial bronchus spreading out between the cartilages. (Hæmatoxylin and eosin.)

(*c*) Very low power of spreading margin of a metastasis in right frontal lobe, showing combined cystic and papillomatous structure. (Mallory's stain.)

(*e*) Margin of one of the cerebellar nodules (Fig. 734, p. 1146), showing the typical papilliferous character often seen in such metastases. (Hæmatoxylin and eosin.)

(*a*) × 75 (*c*) × 25 (*e*) × 75



(*b*) × 75 (*d*) × 75 (*f*) × 300

(*b*) Section of the periphery of the tumour spreading into the surrounding lung-tissue. (v. Gieson's method).

(*d*) High power of same (*c* above) stained for mucin by Mayer's mucicarmine.

(*f*) High power of the same (*e* above), showing the columnar cells suggestive of bronchial epithelium.

3. **Squamous carcinomas** are common, and they appear usually to arise from epithelial cells which have undergone metaplasia as a result of chronic inflammatory or degenerative changes in the bronchi or in bronchiectatic cavities, in which, quite apart from any neoplastic development, this squamous transformation is sometimes also found.

All these varieties of malignant bronchial tumour may infiltrate widely, extending often to the pleura and giving rise to extensive growth on its surface, with hæmorrhagic effusion into the pleural sac. **Metastases** to other parts of the lung itself, in the lymph-nodes, brain, adrenals, liver, kidneys and bone are common. From the root of the lung or from the bronchial lymph-nodes, the growth may invade the mediastinal tissues, pericardium and heart (Fig. 353). Such locally invasive mediastinal spread, sometimes "massive" in character, has in the past, especially when the cells have been of anaplastic or primitive type, not infrequently been described as "mediastinal lymphosarcoma": or, when the cells have been larger, as "endothelioma" of the pleura or lung. **In the brain,**[1] the metastases are almost always multiple, and often of large size, being of most frequent occurrence in the frontal and temporal lobes and in the cerebellum. The only instances in which we ourselves have observed *single* secondary tumours in the brain have taken the form of "malignant cerebellar cysts" (Fig. 738, p. 1149). In middle-aged and elderly males, the clinical results of the cerebral metastases often completely overshadow and obscure the pulmonary symptoms, which, especially in the small and slow-growing types of bronchial tumour, may have been regarded as due merely to "chronic bronchitis" or "asthma" (*see* footnote on p. 516). Just as the prostate should be examined in spinal cases, careful routine examination of the lungs is essential both from the clinical and the pathological points of view in all cases of suspected cerebral tumour, especially when the symptoms include headache, mental confusion, defects of memory and perhaps change of tempera-

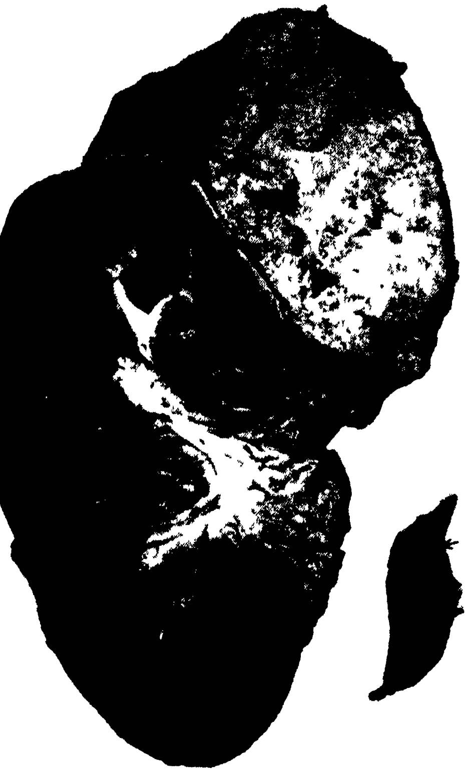


FIG. 352. *Bronchial carcinoma* (Case (D) in Fig. 349): metastasis in suprarenal, one of its common sites. Note the minute secondary growth (marked with the small arrow) in the opposite (right) organ. (W. E. H. case.)

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[1] "Multiple Metastatic Tumours in the Brain arising from Primary Bronchial Carcinoma," by W. E. Carnegie Dickson and C. Worster-Drought, *Journal of Neurology and Psychiatry*, 1936, **16**, 289–320, from which paper most of the illustrations in this section are taken.

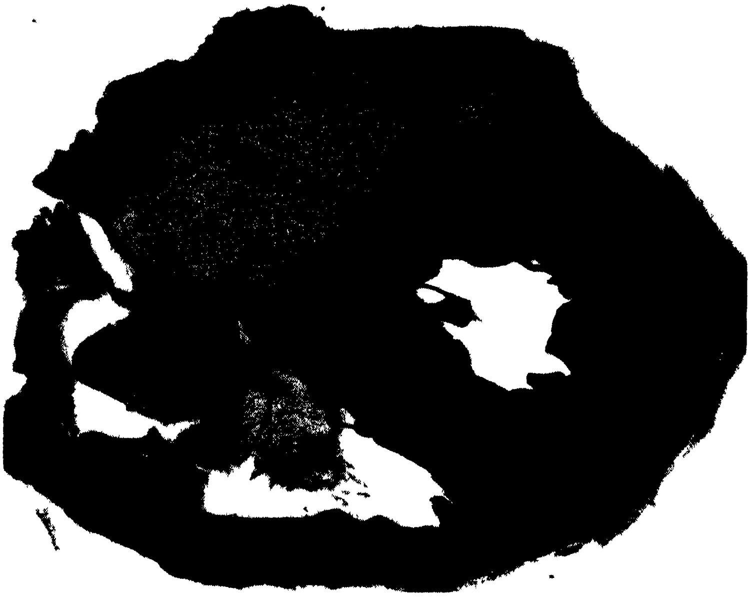
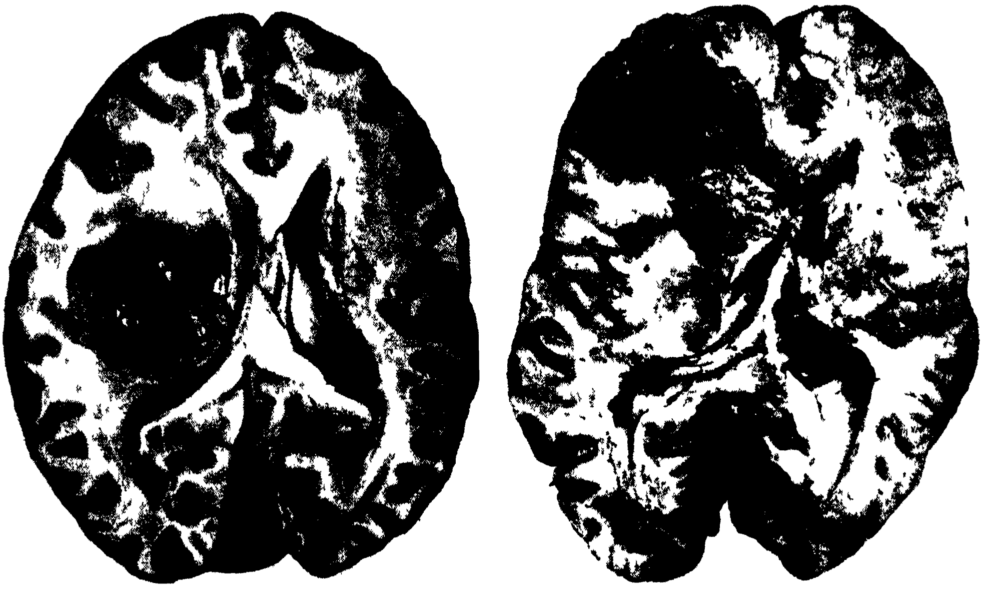


FIG 353. *Bronchial carcinoma* invading heart · horizontal slice through ventricles showing extensive invasion of heart-wall.

ment, together with the presence of papillœdema, and sometimes without definite localising symptoms. In the female, on the other hand, the clinical history more frequently points definitely to the presence of the pulmonary lesion.



(A)

FIG. 354 (A), *Bronchial carcinoma* metastasis (one of several) in brain of a female aged forty years The primary tumour was a so-called "oat-celled" tumour. Note the "mucoid" character of this secondary growth (*cf* Figs 351 (*d*) and 734, pp. 573 and 1146).

(B)

FIG. 354 (B). *Bronchial carcinoma* in a male aged fifty-six large coalescing metastases in left frontal lobe of case D in Fig 349, p 570. The choroid of the right lateral ventricle was also invaded.
(W. E. H. cases.)

All the varieties may show papillomatous structure, especially in their metastases. Cysts often develop in the cerebral and other metastases, and these usually contain mucin (Figs. 351, 354 and 734, p. 1146). The growths may cause considerable obstruction of the bronchi, with resulting widespread collapse of the lung and dilatation of the affected bronchi. The accumulation of secretion may give rise to purulent bronchitis, bronchiectasis and abscesses in the lung-substance. It is doubtful whether carcinoma of the lung ever originates in the cells lining the alveoli or in the mucous membrane of the terminal bronchi; but a type, previously mentioned, having a white solid appearance on section, resembling the grey-hepatisation stage of pneumonia, and a mucoid-looking surface, may have arisen from the alveolar endothelium, especially where that endothelium has become cubical. It should be noted, however, that mucin-secreting cells do occur in the metastases from typical forms of carcinoma of bronchi, and it is at least possible that in such cases the lung-alveoli have become filled with cells from such a tumour and that these cells have undergone a mucinoid change.

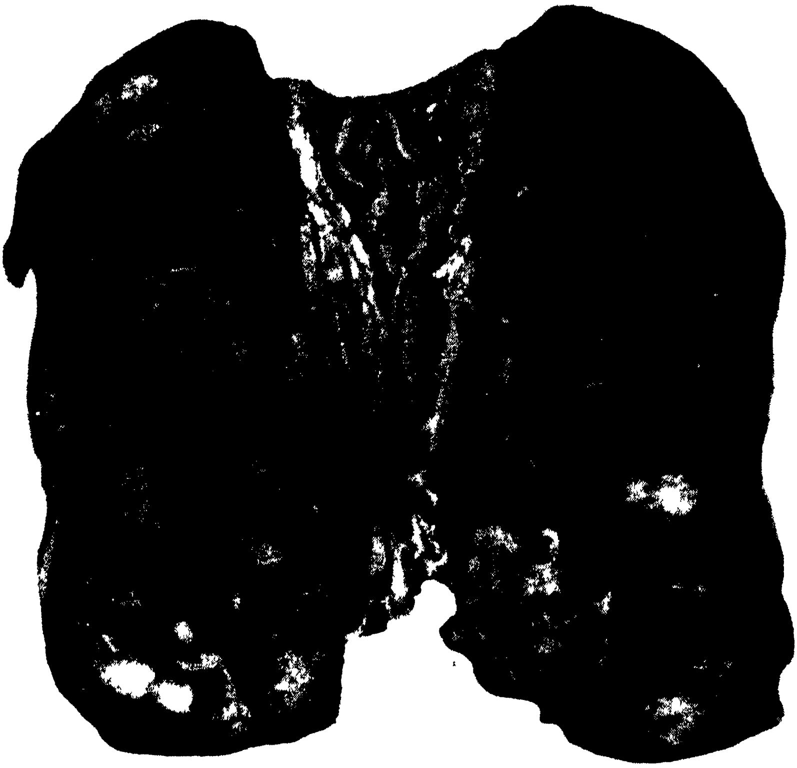


FIG. 355. *Lung.* Multiple secondary nodules of carcinoma, the primary growth being in the kidney, a so-called "hypernephroma"—really a renal adenocarcinoma—in a woman aged 24 years.

Bronchial adenomas, so-called, which appear on bronchoscopic examination as sessile, or more frequently as polypoid, growths, projecting into the lumina of the larger bronchi, often show, on microscopical examination, a structure which can be differentiated only with difficulty from that of adenocarcinomas. They grow slowly and exhibit a tendency to infiltrate at their site of origin from the bronchial mucous membrane. Whether they represent a neoplastic entity or are carcinomas of slight malignancy is still open to discussion, but their clinical recognition is of importance as they often can be treated with success by endobronchial resection if early diagnosis is made.

Secondary tumours, often multiple, are frequently seen in the lung. Direct spread of lymphosarcomas of the mediastinal lymph-nodes into the lung-tissue may occur. The secondary growths of certain tumours of bone, especially sarcomas—because of their tendency to spread by the blood-vessels—and of chorionepithelioma and so-called "hypernephroma" (Fig. 355), have their site of election in the lungs. Mammary cancer may spread to the lymphatics of the pleura and thence to the lung, and abdominal carcinoma may reach the lung by way of the retroperitoneal, mediastinal and bronchial lymph-nodes. As already stated, primary cancer of the lung may itself give rise to extensive and numerous metastases in the lung.

Parasites

Hydatids may be found, especially in the right lower lobe. Of other parasites, the most important are certain lung-flukes (*Paragonimus ringeri*, *P. westermanii*, and *P. kellicotti*), the ova of which are found in the sputum (p. 385). In filariasis, the *Microfilariæ* are found congregated in the blood-vessels of the lung during the periods in which the parasites are absent from the peripheral blood. Abscesses caused by *Entamœba histolytica*, and secondary to dysenteric ulceration of the intestine or to amœbic abscess of the liver, are occasionally found. These conditions are discussed in the section on Animal Parasites (p. 365), as is also the migration of *Ankylostoma*, by way of the lungs and bronchi, on its way from the skin-surface to its habitat, the upper part of the small intestine (p. 411, *et seq.*). The analogous migration of the immature forms of *Ascaris lumbricoides* on their way to their habitat in the intestine is described on p. 409.

SECTION VI

DISEASES OF THE PLEURA

HYDROTHORAX. Normally, the pleural cavity contains only a minimal amount of liquid ; but there may be an increase during the hours before death. Therefore a small amount in the pleural cavities at a post-mortem examination may be of little pathological significance. Larger accumulations, however, in cardiac or in renal disease occur as part of a general dropsy, and to this condition the term "hydrothorax" is applied. This is usually bilateral, though the amount may be larger in one pleural cavity than in the other ; but a unilateral accumulation may occur, as, for example, from pressure on the veins of one side by tumours, or without obvious explanation, as in nephritis, in which such unilateral hydrothorax is sometimes present. The liquid presents the ordinary characters of a serous transudate. The pleura itself may become diffusely thickened and opaque, or even œdematous, as a result of the accumulation, and the lungs may undergo collapse in proportion to the amount of liquid present. When the pleural sac has become obliterated by adhesions, these and the lung-tissue itself may become œdematous by the accumulation of fluid, which would otherwise have produced a hydrothorax.

HÆMOTHORAX. Large hæmorrhages may be due to wounds of the chest-wall or lung in which the blood-vessels have been lacerated : to fracture of the ribs : rupture of aneurysms into the pleural sac : or to degenerative changes in or erosion of vessels in and by tumours. The fluid consists, in the main, of blood, which does not necessarily undergo massive clotting when removed from the chest. Frequently, the lung is collapsed, especially its lower lobe. The portion of the lung above the fluid may show emphysema.

At the upper limit of the effused blood, loose fibrinous adhesions gluing the surface of the lung to the chest-wall are commonly present ; whereas, in the space occupied by effused blood, both the parietal pleura and the collapsed lung become coated with a thick layer of fibrin. The collapsed lung, especially if it is not lacerated, rarely shows evidence of pneumonia or even acute hyperæmia. Infection does not necessarily take place, but may supervene early or late in the process. In cases such as gunshot-wounds where fragments of clothing, etc., are carried into the pleural cavity, the exudate contains many inflammatory cells (polymorphonuclear leucocytes, etc.), the deposit of fibrin on the pleura is more abundant, and there may be a considerable development of gas by gas-producing anaerobes. This gas has an offensive smell, often accumulates under considerable pressure, and may collect above the septic blood. It may become limited by adhesions, or may occur at isolated points in the midst of an infected hæmothorax.

Small subpleural ecchymoses are seen in various forms of infective diseases (*e.g.*, the acute fevers and septicæmias), in " blood-disorders " such as untreated or insufficiently-treated Addisonian anæmia, in purpura, in asphyxia, and in some cases of chronic venous congestion.

PNEUMOTHORAX. The accumulation of air or gas in the pleural cavity, for which this term is used, may be extensive, or localised by adhesions. It may result from the entrance of air through a wound of the chest-wall, a wound of the lung, or erosion or spontaneous rupture of the lung-tissue. The erosion may follow the softening and breaking-down of a septic infarct, or be produced in a minute bronchiectatic or tuberculous cavity which is in direct communication with a bronchus, and from which a communication between the air-tissue of the lung and the pleural cavity is established. Rupture of the lung-tissue may occur during excessive exertion—for example, during the paroxysms of whooping-cough or other severe attack of coughing, especially if the lung is emphysematous : or from the violent concussion or the blast of explosives. The laceration may occur at the site of an adhesion to the chest-wall. Pneumothorax is also, but much less commonly, produced by erosion of a suppurating or tuberculous bronchial lymph-node directly, or by way of a bronchus, into the pleural cavity ; or by the perforation into the pleural cavity of an ulcer of the stomach which has become adherent to the diaphragm, or of a carcinoma of the œsophagus.

One form of pneumothorax may be caused by the gas formed by micro-organisms, usually anaerobes, during life. Henry and Elliott[1] (1916) found that this was the usual type of pneumothorax resulting from gunshot and other wounds of the thorax, and that the presence of air derived from the lung itself was uncommon. No doubt some air escapes through the damaged lung-tissue, but, apparently, this is small in amount and is soon absorbed.

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[1] Herbert Henry and T. R. Elliott, " The Morbid Anatomy of Wounds of the Thorax," *Jour. R.A.M.C.*, 1916, **27**, 525.

The most important complications or sequelæ of this condition are collapse of the lungs, and, especially if septic organisms have been introduced, inflammation, suppuration, or hæmorrhage, with the production of pyo- and hæmo-pneumothorax. Pneumothorax may have a beneficial influence on the course of certain diseases of the lung such as tuberculosis, and is sometimes artificially induced for this purpose.

ACUTE INFLAMMATION (PLEURISY or PLEURITIS) may result from local or from general causes. Among the local causes, the most important is extension of the inflammatory process from adjacent parts—for example, from the lungs in cases of pneumonia, septic infarction, gangrene, or tuberculosis : from pericarditis : from acute inflammatory conditions of the mediastinum, ribs, or chest-wall : from the abdomen, by way of the lymphatics of the diaphragm, in peritonitis or in other abdominal affections ; or it may be due to trauma of the chest-wall or of the lung. In the group of general causes are pyæmia and septicæmia, acute rheumatism and other acute infective diseases, and tuberculosis, in all of which the infective agent—bacteria, toxin or virus—is carried to the pleuræ in the blood. Certain forms are secondary to tuberculosis or cancer of the pleura. When, however, all these causes have been excluded, there still remains a small residuum of cases in which the origin of the infection is obscure. These, until their cause has been ascertained, are classed under the unsatisfactory term " idiopathic " pleurisy. The majority of these are undoubtedly tuberculous in origin, and, if a systematic and thorough examination were made by inoculation into guineapigs and culture, we believe that the number of so-called " idiopathic " cases would be small.

Morbid Anatomy. It is customary to describe various types of pleurisy as dry or fibrinous, serous or serofibrinous, purulent, and hæmorrhagic ; but these are not necessarily independent conditions, and one often passes into another, or they may be found in combination. In chronic cases, an acute attack is often superimposed, and fibrin may be deposited on the already thickened pleura, or in the substance of adhesions, if these are present ; or an attack may arise in those parts of the sac which have not been obliterated by a previous infection.

In the early stages of the process, the usual phenomena of inflammation—dilatation of vessels, exudation of lymph and emigration of leucocytes—are observed. If the exuded lymph is small in amount and its coagulative power high, it will be deposited as fibrin on the surface of the pleura, at first as a thin white or greyish pellicle which soon becomes yellowish and increases considerably in thickness. The deposit may be confined to localised areas of the pleura, or may involve both visceral and parietal surfaces, and, if the exudate does not separate the inflamed surfaces, adhesions are formed between them or between the adjacent layers of the visceral pleura lining an interlobar sulcus. This is the condition described as **" dry " or fibrinous pleurisy** If the exudate is abundant and has been produced rapidly, the **serous or serofibrinous type** or **" pleurisy with effusion "** occurs. The sac may be distended and filled almost completely with fluid, the lung being pressed backwards and inwards towards its root, and becoming collapsed; whilst the heart and pericardium are displaced towards the middle line or to the opposite side of the chest. The pleura itself shows a more or less extensive coating of fibrinous exudate. If the serous exudate is formed rapidly, it is less albuminous in character, its coagulative power is lessened and it resembles dropsical fluid. Leucocytes may be scanty or numerous. Their types vary with the nature of the cause and the acuteness of the process. Thus, in the pleural inflammations caused by pyogenic organisms, *e.g.*, pneumococci, staphylococci, or streptococci, the polymorphonuclear leucocytes predominate in the early stages; whereas, in those caused by the tubercle bacillus, the lymphocytes or cells indistinguishable from them are the principal and characteristic cells present, and occasional cases in which eosinophils predominate have been described (pp. 26 and 599). Again, in more chronic inflammatory cases, the proportion of mononucleated cells of various kinds is considerably increased (*see* Inflammation, p. 27 *et passim*) If the neutrophil leucocytes are numerous and the causal bacteria pyogenic, degenerative changes will be present in the cells and the exudate will be purulent—**purulent pleurisy** or **empyema.** The suppurative process may spread directly from the lung in cases of acute lobar pneumonia, septic infarction, bronchiectasis, abscess of the lung, or tuberculosis, especially where a cavity has opened into the pleural sac. Empyema may also be secondary to diseases of the chest-wall, *e.g.*, of the ribs, and occasionally of

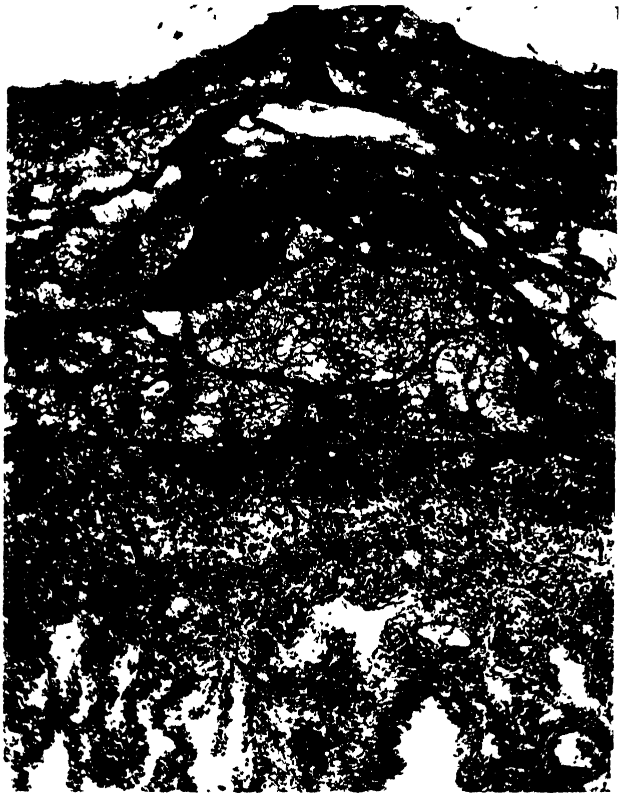

FIG. 356. *Acute Pleurisy.* Showing a deposit of fibrin and leucocytes on the surface of the pleura. × 60.

the vertebræ: or to peritonitis or any suppurative condition below the diaphragm in connection with the liver, spleen, stomach, or intestines; or it may arise in the course of pyæmia, the infective agent being carried by the blood-stream to the tissues in the neighbourhood of the pleura, the pleura itself and frequently the lung. Of the organisms present, either alone or in association with one another, the commonest are the pneumococcus and the *Streptococcus pyogenes*. The pus is found at any part of the pleural cavity, but its commonest situation is over the lower and outer aspect of the lower lobe. Sometimes it is confined to the surface of the diaphragm or to an interlobar sulcus (Fig. 311, p. 532). Occasionally the purulent fluid has a foul odour, and in such cases gas and various anaerobic bacteria are usually present. Sometimes the exudate may consist of almost pure blood, a condition associated especially with tuberculous and malignant diseases of the lungs and pleura; and it may be hæmorrhagic in some cases of nephritis, in certain blood-disorders, in scurvy and other conditions of malnutrition. In malignant disease, tumour-cells are sometimes recognisable in the fluid; but, unless they occur in distinct clumps and masses exhibiting tissue-structure, it is often difficult or even impossible to distinguish them from some of the mononucleated cells which are present in the exudate in cases of non-malignant pleurisy.

Sequelæ of Pleurisy with Effusion and of Empyema:—

The fluid may be **absorbed** naturally or removed by operation. If this does not occur, **organisation,** with the formation of connective tissue, takes place, uniting the chest-wall and lung more or less completely, or forming fibrous bands of varying lengths between the visceral and parietal layers of the pleura. If these adhesions are not formed, the organisation results in a chronic fibrous thickening, especially of the visceral pleura. **Collapse** of the lung is present to a varying degree, depending on the amount of fluid, and on the presence and extent of the adhesions. When **pus** develops, it sometimes **burrows,** especially along the lines of the intercostal spaces, and accumulates in the subcutaneous tissues of the thorax: or it may make its way downwards between the pillars of the diaphragm, and form an abscess round the kidney, or it may even reach the surface and discharge in the inguinal or gluteal regions. When thus "left to its fate," such spontaneous discharge of the pus is sometimes referred to under the rather old-fashioned term "*empyema necessitatis*". **Perforation into the lung** and partial evacuation of the contents through a bronchus may take place, giving rise to purulent expectoration, with inflammation in both the bronchi and the tissue of the lung. Air sometimes enters the pleural cavity by this new channel, and gives rise to **pyo-pneumothorax**; and, if putrefactive bacteria gain admission, the pus assumes a very putrid character. Broncho-pleural fistulæ are, however, produced more frequently by the reverse process of rupture of a pulmonary lesion into the pleural cavity. The end-result is much the same in either case. The liquid portion of the pus may undergo absorption, leaving inspissated caseous material which becomes **calcified,** and —the pleura becoming greatly thickened—re-expansion of the collapsed lung, which has become extensively fibrous, is prevented. The chest-wall is dragged in, and the pericardium and heart, as well as the opposite lung, may be pulled across the middle line.

Chronic Pleurisy. This term is generally applied to a fibrous thickening of the visceral layer of the pleura, the result of repeated acute attacks, or of the proliferative and protective process which is found especially in chronic tuberculous disease of the lung.

Localised chronic fibrous thickenings of the pleura have been described under the various forms of chronic interstitial pneumonia. They are common in elderly people, and occur especially at the points where the interlobular septa meet the deep layer of the pleura. They are formed around accumulations of pigment, or of other foreign material such as stone-particles.

Tuberculosis of the Pleura. *See* Granulomata, p. 65, and Tuberculosis of Lungs, p. 550 *et seq.*

TUMOURS

Primary tumours of the pleura itself, as distinct from those of the lung, are rare. Fibromas, lipomas, chondromas, osteomas, sarcomas (especially the spindle-celled variety), and cancer, have been described. Primary mesotheliomas (endotheliomas), starting in the lymphatics of the deep layer of the pleura from the surface lining-cells, may cause a diffuse thickening over a wide area of the pleura ; but the pleura may be involved by the spread to it of malignant tumours of the breast, chest-wall, mediastinum or lung, whether these be primary or secondary. Some cases, originally described as " endothelioma " or " mesothelioma " of the pleura have, on re-investigation, proved to be secondary extensions or metastases of so-called " oat-celled carcinomas " of the bronchi (p. 571).

PARASITES

Echinococcus-cysts (hydatids) are the only important parasites found in the pleural cavity (pp. 400–405).

CHAPTER XVIII

DISORDERS OF THE BLOOD AND DISEASES OF THE BLOOD-FORMING ORGANS

SECTION I

Introductory. The physiology and pathology of the blood have now become such extensive fields of specialised knowledge and research that textbooks on hæmatology must be consulted by those who wish to study them in any detail.[1] In the past, attention has been devoted chiefly to the morphological characters of the formed elements of the blood—the varieties of leucocytes, normal and abnormal, their total and their relative numbers, and any degenerative or other changes affecting them : the numbers, size, shape, and hæmoglobin-content of the red corpuscles or erythrocytes : the numbers of the blood-platelets, and similar phenomena. More recently, considerable work has been done in connection with the physics and chemistry of the blood, and also with regard to its bacteriology and parasitology. Of great importance is the presence, not only of the hormones secreted into it by the ductless glands, but also of certain specific substances which are either found normally in the blood, or are developed in it as the result of disease—natural or experimental—and which are known as hæmolysins, agglutinins, precipitins, coagulins, opsonins, bacteriolysins, etc. The chemistry and nature of these bodies are still little understood, and their presence can be determined only by certain delicate biochemical and other tests which are still to a large extent empirical in their working and results. An account of some of these substances and their reactions is given in the Section on Immunity (p. 127 *et seq.*).

The Total Volume of the Circulating Blood. The earlier estimate that, in man, the total amount of blood was about one-thirteenth of the body-weight, has, by more recent methods, been found to be excessive. Haldane and Lorrain Smith estimated the average amount at 4·78 per cent., or about a twentieth (with variations of from about a thirtieth to a sixteenth), but an exact determination has not yet been successfully made, though various colorimetric and dilution-methods have been suggested, and are more accurate than the older procedures. The rapid **diminution** in the total intra-vascular volume of the blood in **shock**, and its resulting concentration from loss or transference of fluid into the tissues owing to the increased permeability of the capillaries, is described on p. 183. The degree of such concentration can to some extent be estimated from the resulting variations in the hæmoglobin-estimations and erythrocyte-counts. If the total fluid bulk of the blood is artificially increased or diminished, rapid readjustment as regards volume takes place. It has been estimated that, in the adult, the combined surface of all the red corpuscles in the body is over 3,000 square metres or 3,600 square yards (about three-quarters of an acre). This will therefore be the approximate amount of " interface " between corpuscles and plasma available for the interchange of gases and other substances during respiration, adsorption and other processes in which both take part.

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[1] L. E. H. Whitby and C. J. Britton, " Disorders of the Blood," 4th edition, 1942 : and, for the chemical aspects of the subject, G. A. Harrison's " Chemical Methods in Clinical Medicine," 2nd edition, 1937, will be found useful for this purpose. Much interesting information will also be found in Samson Wright's " Applied Physiology," 7th edition, 1940. Our readers are also asked to study the note upon " The Reticuloses and Reticulo-Endothelioses " on pp. 1262–4 at the end of our textbook.

The Sedimentation-Rate of the Erythrocytes ("E.S.R."), *i.e.*, the rate at which they fall to the bottom of a standard calibrated tube,[1] is found to be accelerated in certain conditions associated with inflammation or tissue-destruction, more particularly in active tuberculosis and rheumatic conditions ; and. although in no way specific, the test is of some diagnostic and prognostic value, more especially in judging the progress of cases under treatment.

The Chemistry of the blood is extremely complex, and little is yet known of the ultimate nature of many of its constituents. In the blood-plasma or liquid portion of the blood are dissolved or suspended—in addition to innumerable other substances—the nutrient material which it conveys to the tissues, and the various waste-products which arise during metabolism, and are carried to certain organs to be destroyed or excreted. Similarly, as just noted, the internal secretions or hormones elaborated by various organs and tissues are distributed by the blood and lymph, through the agency of which they act upon other structures of the body.

The blood is constantly changing in its composition. The relative amount of fluid and the absolute and relative numbers of the formed elements per unit of volume vary, not only in different individuals, but also from time to time in the same individual and in different organs and tissues of the body. Thus, in the interpretation of observations upon the blood, many considerations have to be borne in mind, and the results of its examination are to be interpreted only in the light of the fullest possible clinical information. Moreover, it must be remembered that with blood-counts the range of experimental error is always appreciable but can be limited by the averaging of several separate observations and estimations of each item in the examination, as well as by careful control of the conditions under which the blood is collected as regards time of day and relation to sleeping and waking, food, fluid-intake, etc. For purposes of comparison, blood should be collected under as precisely similar conditions on each occasion as is practicable. We find that coverslip-preparations give more uniformly accurate differential counts than "drawn" or "pushed" films on slides.

The blood contains from rather more than one-third to one-half its weight, and approximately half of its bulk or volume,[1] of corpuscles, and from 20 to 25 per cent. solids. The **blood-plasma** is resolved, on coagulation, into serum and fibrin. The **serum** contains 8 to 9 per cent. solids, of which 7 to 8 per cent. are proteins and about 1 per cent. salts. The protein-content of the serum consists chiefly of the two series of coagulable proteins, the **serum-albumins** and the **serum-globulins**, which can be separated by dialysis, the globulin-fraction being divisible into two further fractions—**euglobulin** and **pseudoglobulin.** The serum-globulin molecules are of large size and will not pass through a fine unglazed porcelain filter ; nor, under normal conditions, do they pass through the choroid plexuses into the cerebrospinal fluid, though, in certain pathological states of these plexuses and of the pia-glial limiting-membrane (pp. 953, 962–3, and 995), and of the capillary endothelium of the cerebral vessels,[2] they may do so in varying degree. These large globulin-molecules are probably of importance in relation to various "adsorption" phenomena. The albumin-content of the serum is considerably diminished in severe anæmias and in dropsy; and, in renal disease, the smaller size of the molecules of serum-albumin may allow of their passage through the damaged glomeruli into the urine (p. 877).

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[1] This is conveniently measured by the technique devised by Wintrobe, viz. in a suitable sample of freshly collected oxalated blood first observing the sedimentation rate of the erythrocytes in a calibrated and graduated 100-mm. tube, and then recording the packed volume of the corpuscles after centrifugalisation in the same tube, as well as the amount of the supernatant plasma, all the figures being recorded in millimetres, which thus give percentage-readings. A correction of the sedimentation-rate is required if any appreciable degree of anæmia is present.

[2] The "Blood-Brain Barrier," *Brit. Med. Jour.*, Annotation, 1942, ii, 703.

Traces of numerous nitrogen-containing substances such as **urea** (normally 15 to 40 mgr. per 100 c.cm.), **uric acid,** etc., are present in the blood and may be increased in acute fevers, uræmia, polycythæmia and leukæmia.

Glucose in small quantity is normally present (fasting level in health 80 to 120 mgr. per 100 c.cm.), and is increased much above the normal renal threshold of 180 mgr. per 100 c.cm. in diabetes mellitus, in which, however, its amount varies greatly (p. 800 *et seq.*). Hypoglycæmia, on the other hand, results from hyperplasia or from tumour-growth of the islet-tissue of the pancreas.

Glycogen in the plasma and in the leucocytes can be demonstrated microscopically by its brown staining-reaction with iodine. In finely granular form, it is normally present in the plasma; whilst it is found also, sometimes in large amount, in the leucocytes, particularly the neutrophil polymorphonuclears (**glycogenic reaction** to iodine), in cases of fever, in acute inflammatory and suppurative diseases, in septicæmias, and in certain toxæmic conditions. In tuberculosis, the glycogenic reaction of the leucocytes is said to occur only if there are suppurative complications: and in diabetes, only if coma, suppuration, or gangrene has supervened—though, in diabetes itself, the **extracellular** glycogen in the blood-plasma is usually increased.

Fatty Substances. These vary considerably in amount in different individuals, and also with the quantity of fat ingested and absorbed. **Lipæmia,** or abnormal increase of fat in the blood, occurs in certain cases of diabetes (p. 802). Such blood, when freshly drawn, shows a milky pinkish colour, and, on standing, separates into various strata, the supernatant fatty layer often being of considerable thickness.

Bile-acids, bile-pigment, and also, **cholesterol,** are present in considerable amounts in cholæmia or jaundice (p. 228 *et seq.*: and *cf.* p. 788).

Various **inorganic salts,** such as phosphates, chlorides, carbonates, and sulphates, are normally present in the blood-plasma. Of these, sodium phosphate and chloride are present in greatest amount. Calcium phosphate is an important constituent of blood-plasma, in which it exists in diffusible and non-diffusible fractions, the former being ionised and the latter non-ionised, and the average total amount in health being 9 to 11 mgr. per 100 c.cm. A reduction of the calcium-content of the blood is of importance chiefly in tetany and rickets, but disturbances of the content may occur in nephritis, hyperthyroidism and osteomalacia. It is increased in cases of hyperparathyroidism due to parathyroid tumour (generalised osteitis fibrosa, pp. 837–8 and 1211).

Physical Characters of the Serum. The normal pale-yellow or slightly greenish-yellow tinge of the blood-plasma and the resulting serum is due to the presence of certain fatty pigments or lipochromes, which may be increased or diminished in various pathological states of the blood. In acute toxic diseases characterised by blood-destruction, the blood-serum may present a reddish tint, due to the presence of hæmoglobin extravasated from the injured red corpuscles. This is, however, as a rule only slight in amount, and, in such toxic conditions, the colour is more usually orange-red from the presence of bilirubin.

Osmotic Tension. When the osmotic tension of the salts in the plasma is normal, the hæmoglobin in the red corpuscles is retained within them ; but, if this relationship is sufficiently altered by the addition of water, the corpuscles become "laked," *i.e.*, the hæmoglobin passes out into the plasma. In terms of the strength of a solution of common salt, the osmotic tension of the blood-plasma is about 0·9 per cent. ; and, by exposing the washed corpuscles to graded and diminishing strengths of salt-solution below that degree of concentration, any increased degree of **resistance** or of **fragility of the corpuscles** can, in a given condition, be tested and estimated. Such alterations are believed to depend largely upon the **shape** of the corpuscles. In certain diseases, these become more globular, a condition known as "**spherocytosis**" (pp. 658–9). The corpuscles are then found to be more vulnerable to the action of *hypo*tonic salt-solutions ; and it has also been established that such solutions, by producing increased endosmosis through the envelope of the corpuscles, cause these to become more globular. Thus the two processes react upon one another, and, at a certain point during this change of shape, the corpuscle ruptures like an over-distended bubble, the enclosed hæmoglobin escapes, and the blood becomes "laked." In the syndrome known as "hæmolytic anæmia" (p. 655 *et seq.*), it is believed by some observers that this increased globularity or spherocytosis is brought about by the injurious action of hæmolysins in the blood. These hæmolytic phenomena in the circulating blood and also the reactions and alterations in the shape of the

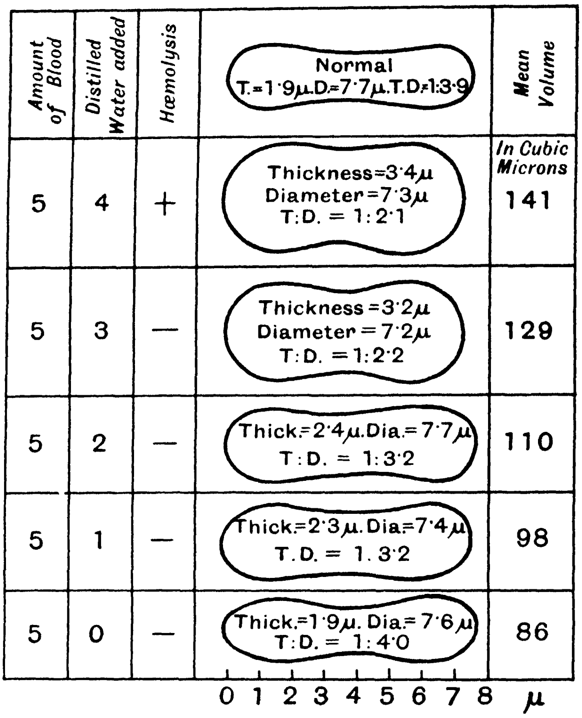

FIG. 357. Changes in the shape and in the diameter, thickness and volume of the mean erythrocyte of normal blood on the addition of the varying amounts (in c.cm.) of distilled water to the plasma (after Haden).

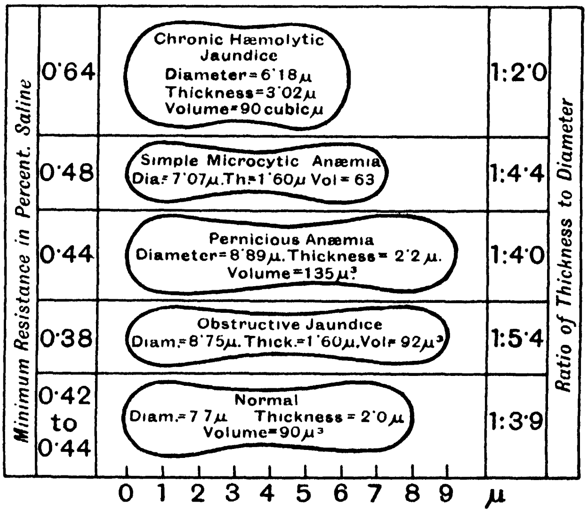

FIG. 358. Cross-section and measurements of the average erythrocyte in various clinical conditions compared with normal (after Haden).

erythrocytes both *in vivo* and *in vitro* have been investigated by Dameshek and Schwartz (pp. 656–7 *et seq.*), and also by Haden [1] and others, and will be most easily understood by referring to Haden's explanatory diagrams (Figs. 357 and 358). From the ratio of the thickness of the corpuscles to their diameter, and also from the volume-thickness index of the average-sized erythrocyte in health and in various diseased conditions, Haden has determined the point at which rupture and hæmolysis tend to commence.

Alkalinity.[2] Problems connected with the relative degree of alkalinity of the blood, *e.g.*, variations, if any, in ketosis, ketonæmia and ketonuria (p. 802), and the general subject of the acid-base equilibrium of the blood, are discussed in books on chemical pathology.

Coagulability. The investigation of the coagulability of the blood is a matter of considerable importance in connection with the various " bleeding-diseases," such as scurvy, purpura hæmorrhagica, and hæmophilia or the so-called " hæmorrhagic diathesis." In some of these conditions, coagulation may be indefinitely delayed, whilst in others the increased tendency to bleeding is due to aberrations in the walls of the blood-vessels, including the capillaries, some of them brought about by vitamin-deficiencies (*e.g.*, a vitaminosis-P or deficiency of the " citrine " element of lemon-juice, etc.—p. 443) : rather than to any observable deficiency in the number or character of the blood-platelets. Coagulation may be delayed in acute infective fevers, in some of the anæmias, and in cases of jaundice. As stated on p. 161, the coagulation of shed blood is brought about by the production of **fibrin** by the action of **thrombin** upon the **fibrinogen** present in the plasma. Thrombin itself is *not* present as such in the blood, but is produced by the interaction of **prothrombin** with **calcium salts** under the stimulating influence of the ferment **thromboplastin** (p. 161) which is liberated from the blood-platelets when these find themselves in abnormal surroundings ; and until this ferment is liberated from the platelets there is no union between prothrombin and calcium-ions and therefore no formation of thrombin. For W. H. Howell's views on the action of heparin as " a natural physiological anti-coagulant," and its function in preserving the fluidity of the blood and certain of the body-fluids, *see* p. 162 and footnote reference to the work of Jorpes on that page, and *see also* pp. 599–600.

Prothrombin itself requires for its formation the presence of **vitamin K** (pp. 161 and 442) in sufficient amount in the diet (it can be artificially prepared, *e.g.*, from spinach), together with **bile-salts** which are required for the absorption of vitamin K from the intestine. The absence of either of these will lead to a **" hypothrombinæmia "** (p. 161). Even although fibrinogen, calcium-salts and thromboplastin (thrombokinase) are present in the blood, no thrombosis can take place in the absence of thrombin (thrombase). The blood of young infants, especially on or about the third day after birth, is deficient in prothrombin, and the occurrence of **neo-natal intracranial hæmorrhage** (pp. 442 and

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[1] " The Mechanism of the Increased Fragility of the Erythrocytes in Congenital Hæmolytic Jaundice," by Russell L. Haden, Cleveland, Ohio, *The American Journal of the Medical Sciences*, 1934, **188**, 441–449. For a note on the spherocytosis supervening in the erythrocytes of blood stored for transfusion, *see* p. 595.

[2] Samson Wright (*loc. cit.*, p. 563) gives the average H-ion concentration of the blood, using the hydrogen-electrode method, as, according to Van Slyke, about *p*H 7·25, or, according to Dill, as varying between 7·36 and 7·44. (In Sørensen's notation, the *p*H of pure neutral water is represented by the figure 7.)

1036) can in many instances be prevented by the administration of vitamin K in sufficient quantity, reducing its incidence, in one large series in America, from nearly 10 per cent. to only 1 per cent. In **hæmolytic** and **obstructive jaundice,** the missing link is the **absence of the bile-salts from the intestine,** where they are needed for the absorption of vitamin K ; and this non-absorption of the latter into the blood prevents the formation of prothrombin, hinders coagulation and encourages hæmorrhage. The administration of vitamin K does not, however, prevent the bleeding in hæmophilia (*see* below).

In various diseases, hæmorrhage may be due to the loss of the power of coagulability owing to the absence of one or more links in this complex chain. **Hypoprothrombinæmia** (p. 161) is believed to be the specific predisposing cause of hæmorrhage in the new-born infant (*see* above). Similarly, in any form of obstructive jaundice associated with the retention of bile-salts, serious hæmorrhage may occur during or after a surgical operation, *e.g.*, for the removal of obstructing gall-stones : or even from some less serious traumatic cause such as the extraction of a tooth. It has also been thought by some that in jaundice an additional factor in the prevention of thrombosis may be that the calcium in the blood becomes united with the retained bile-pigment, and is thus rendered unavailable for union with the prothrombin. In **hæmophilia,** prothrombin, fibrinogen, and calcium-ions are all present, but the **platelets** or **thrombocytes** are said to be unduly **resistant** to disintegration, and hence do not sufficiently readily give rise to thromboplastin ; or again, in so-called "**essential thrombocytopenia**" (pp. 669–670), there is deficient formation of the platelets themselves. Some of these suggested explanations still lack full confirmation, and the whole subject requires further investigation.

The **coagulability** of the blood can be estimated by the length of time taken for drawn blood to coagulate. Lee and White recommend drawing off 1 c.cm. of blood from a vein into a dry syringe and transferring it to a clean dry test-tube 8 mm. in diameter, plugging with a rubber-stopper, and inverting (or preferably merely gently tilting) the tube every half-minute until the blood is found to have become firmly clotted. Another rough and ready but convenient method is repeatedly to draw the eyed-end of a needle through a drop of freshly-drawn blood on a slide until the formation of definite fibrin-threads is observed; or capillary glass-tubing of sufficient length may be rapidly filled with blood and gently broken across at regular time-intervals until clotting is found to show between the broken ends. Normally the **coagulation-time,** or, more accurately, the **clotting-time** at 37° C. varies from five or six to ten minutes, or at room-temperature (20° or 21° C.) a little longer, when estimated by these methods. Whichever method is employed, a control-experiment with a normal blood should always be carried out in order to check any errors introduced by slight variations of conditions and technique—and whether the blood has been obtained from capillaries or a vein should be recorded.

In suppurative lesions, especially those due to the pneumococcus, and also in acute lobar pneumonia produced by that organism, fibrinogen is increased in the blood, as are also the platelets because of the stimulation of the megakaryocytes along with the leucoblastic tissues in the bone-marrow ; and coagulation is therefore more rapidly produced than under normal conditions. Intracardiac thrombosis is thus an important complication of acute lobar pneumonia. Increased liability to thrombosis is also described in chlorotic anæmias (pp. 642–4).

Fibrolysin-Test. The resistance of the plasma-clot of drawn blood to the softening or digestive action of hæmolytic streptococci has been investigated in various disorders, and has been found to be **increased** in rheumatic and typhoid fevers, pneumonia and in septic conditions generally.

Various Ferments, oxidising, fat-splitting, glycolytic, etc., occur in the blood.

Hæmagglutinins and Hæmolysins in the Blood :—

There are four main types or groups of human blood, a knowledge of which is essential for all who perform transfusion of human blood as a preliminary to any serious operation, or in Addisonian anæmia, hæmophilia, septicæmia, etc., or, particularly in wartime, for the treatment of hæmorrhage. Quite apart from the risk of transmitting diseases such as syphilis or malaria, serious results can follow the intravenous injection of " incompatible " blood—vomiting, dyspnœa, urticarial skin-eruptions, rapid feeble pulse, and, perhaps convulsions or coma, and, in some cases, death. In order to minimise these risks, tests must always be carried out to ascertain that the donor's red corpuscles (*a*) **will not be agglutinated,** and (*b*) **will not be hæmolysed,** by the plasma of the recipient—the two phenomena usually running parallel with one another. In other words, **a compatible blood is one in which the donor's erythrocytes are neither agglutinated nor hæmolysed by the plasma** (nor *in vitro* **by the serum**) **of the recipient.**

The **four main blood-groups** differ from each other in their agglutinating properties, and it is assumed that, in the red corpuscles of different individuals there may be present (or absent) certain **agglutinable substances,** the **agglutinogens A** and **B** (which are transmitted from parent to offspring as Mendelian dominants) : and in the serum there may be present (or absent) two corresponding **agglutinins,** α and β. Each of the blood-groups therefore possesses a " formula " and these may be expressed as follows :—

Group.			Corpuscles.	Serum.	Formula.
International designation[1]	Moss	Jansky.			
AB	I	4	Agglutinogens A and B	Agglutinin *o* (neither)	AB*o*
A	II	2	,, A only	,, β only	Aβ
B	III	3	,, B only	,, α only	Bα
O	IV	1	,, *O* (neither)	,, α and β	*O*$\alpha\beta$

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[1] Note : in these tables " A " and " B " are capital letters, but the " *O* " is in reality the cypher, " nothing," signifying neither A nor B. To emphasise this we have italicised it thus : " *O* " and also the smaller cypher, " *o*," in the last two columns. There is reason to believe that some of these groups, *e.g.*, the A group, may be further divisible, and an A_2 group (*i.e.*, with blood containing an A_2 antigenic factor or agglutinogen) has recently been described. Yet another agglutinogen, " Rh," has been discovered experimentally in the blood of ***Rhesus*** monkeys, and, in America, found to be present in about 85 per cent. of white people. If, as occasionally occurs—but apparently only in the blood of Rh— (Rh minus) persons—iso-antibodies for the Rh antigenic factor are present in the blood of Rh— recipients, post-transfusional reactions may occur if these persons are transfused with Rh+ blood, especially if the transfusion be repeated a second time (*cf.* p. 135)—but also, even on first transfusion, in the case of Rh— women to whom Rh+ blood has been administered for the treatment of parturitional or post-partum hæmorrhage. In this connection it may be added that the mother's blood may *become* incompatible with that of her fœtus if the latter contains antigenic bodies inherited from the father which are absent in the mother's blood. It has been suggested that hæmolysis of the fœtal red corpuscles may be produced, in the disorder known as erythroblastosis fœtalis, by the passage of the mother's newly-developed agglutinins through the placenta.

The interactions between the serum and corpuscles of the various groups may be summarised as follows :—

Serum of group.	Red blood-corpuscles of group.				Approximate frequency of group among European population.
	AB I (Moss). 4 (Jansky).	A II (Moss). 2 (Jansky).	B III (Moss). 3 (Jansky).	*O* IV (Moss). 1 (Jansky).	
AB 1 (Moss) 4 (Jansky) } Agglutinin *o*	–	–	–	–	5%
A II (Moss) 2 (Jansky) } Agglutinin β	+	–	+	–	40%
B III (Moss) 3 (Jansky) } Agglutinin α	+	+	–	–	10%
O IV (Moss) 1 Jansky) } Agglutinin $\alpha+\beta$	+	+	+	–	45%

+ Agglutination. — No agglutination.

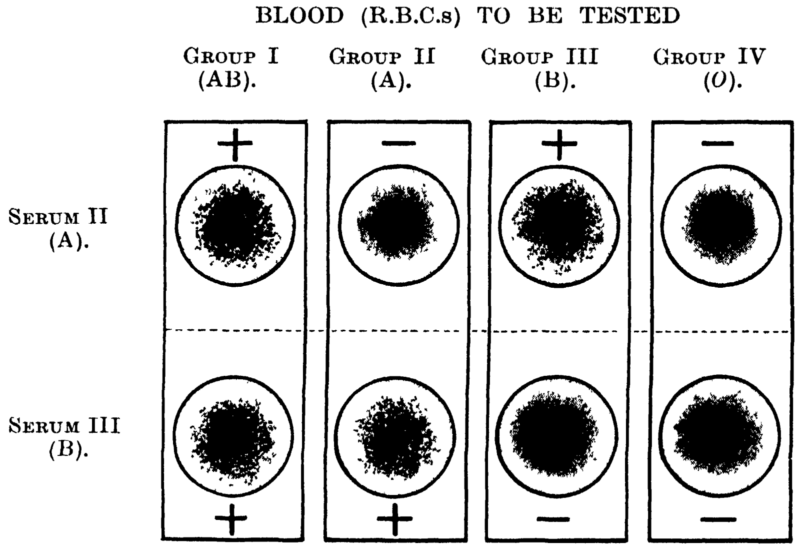

FIG. 359. DETERMINATION OF BLOOD GROUPS.

These four pairs of reactions correspond with those shown in the two centre horizontal rows in the above table, which indicate why any given pair is sufficient to determine the group of the blood tested.

Group I (AB) can **receive** blood from Groups I, II, III and IV (AB, A, B and *O*).
„ II (A) „ „ „ „ „ II and IV (A and *O*).
„ III (B) „ „ „ „ „ III and IV (B and *O*).
„ IV (*O*) „ „ „ „ Group IV only (*O* only).

Group I (AB) can **give** blood to Group I (AB) only.
„ II (A) „ „ „ „ Groups I and II (AB and A).
„ III (B) „ „ „ „ „ I and III (AB and B).
„ IV (*O*) „ „ „ „ „ I, II, III, and IV (AB, A, B and *O*).

Compare these with the results shown in the *horizontal and vertical* rows respectively of the table and diagram.

For the purpose of blood-transfusion work in clinical practice, the important point is that the donor's red blood-corpuscles *must not* be agglutinated by the blood-serum of the recipient, and consequently, when using the Moss method of classification, reference can be made to the foregoing diagram and short tables.

Thus group-I patients are known as universal recipients, whilst group IV denotes those who are universal donors. Nevertheless, it has been shown that the greatest safety is to be attained by the use of donors of the **same** group as the patients who are to be transfused.

In practice, blood-groups are determined by using stock-sera of groups II and III (Moss classification), as these serve to identify corpuscles as belonging to any group according to the following table, which, it will be seen, corresponds with the foregoing diagram (Fig. 359) and the **two middle horizontal lines** in the table above it :—

	Corpuscles :—			
Moss Classification.	I (AB)	II (A)	III (B)	IV (*O*)
Serum II (A) . . .	+	—	+	—
Serum III (B) . . .	+	+	—	—

As a further precaution against error arising from such an indirect method of testing, the **direct matching test** between the serum of the recipient and the donor's corpuscles must also be made before the actual transfusion is performed.

Blood-grouping methods are utilised also in medico-legal work, since it may thus be proved whether a given blood *could be* (but not of necessity *was*) derived from a particular person, or whether two blood-stains *could* have been derived from one and the same person. Further use has also been made of such tests, which include also those for the two additional agglutinins, M and N, for the determination of non-paternity. In every instance, these tests are of limited value except that they may in certain cases determine absolutely *against* paternity. It has been found that the **seminal fluids** of different individuals also fall into four analogous groups.

The Presence of Bacteria in the Blood (*e.g.*, in typhoid and paratyphoid fevers, streptococcal and other septicæmias, pneumonia, etc.), can be demonstrated satisfactorily only by methods of culture. Enough blood—usually at least 5 or 10 c.cm.—is withdrawn from a vein with the strictest aseptic precautions, added immediately to some suitable fluid culture-medium in sufficient dilution (for instance, 5 c.cm. of blood added to at least 25 c.cm. or preferably *more* of nutrient broth), incubated, and examined, microscopically and by sub-culture. In some instances, *e.g.*, in certain streptococcal infections, a positive result is obtained only after prolonged incubation.

The Presence of Animal Parasites, *e.g.*, protozoa, worms, etc., is dealt with in the Chapter on Parasites. (*See under* Malaria, Trypanosomes, Filaria, etc.).

SECTION II

VARIATIONS IN THE FORMED CONSTITUENTS OF THE BLOOD:

THE ERYTHROCYTES OR RED CORPUSCLES

Introductory Note. In considering the origin and development of the red corpuscles in the bone-marrow, the conception comprised by the term "erythron," introduced by A. E. Boycott, of University College, London, in 1929, is useful. Excluding its most primitive progenitors, *i.e.*, the original angioblastic and hæmatoblastic reticulo-endothelial cells, the **erythron** as a developmental unit may be defined as including the **megaloblast** and the subsequent stages of its development into the derivative cells, the **early** and **late,** but still comparatively immature, **macroblast** (or **intermediate erythroblast**[1]), the **normoblast,** the **reticulocyte,** and finally the mature **erythrocyte**—the **normocyte** or **red corpuscle** proper.

This process of development and maturation is dependent upon many factors, such as suitable and adequate supplies of food containing sufficient quantities of the "extrinsic factor" and iron in assimilable form, as well as a trace of copper, vitamins (especially vitamin C) and hormones (p. 640 *et passim*); but more particularly upon the action of the specific **hæmopoietic principle** stored in the liver (p. 647 *et seq.*). Under the influence of this principle, the megaloblast is enabled to undergo the subsequent stages of its transformation to macroblast and normoblast. During the process, it assimilates iron and becomes hæmoglobinised, loses its nucleus and finally passes out into the circulation as the mature oxygen-carrying erythrocyte or red corpuscle. In the course of healthy development, the megaloblasts do not as such become hæmoglobinised, but divide by mitosis to form the next stage in the evolution of the erythron—the **macroblast** (or **intermediate erythroblast**).[1]

The **megaloblast** was described originally by Ehrlich as a large, primitive, nucleated, but hæmoglobin-containing, cell found normally in the bone-marrow and blood of the embryo and fœtus: and then, except for a few days after birth, found later only under pathological conditions. Modern hæmatologists, however, especially of the American school, have departed from this original conception, and define the megaloblast as a large, primitive, nucleated cell with deeply basiphilic cytoplasm which **does not yet contain hæmoglobin** (Fig. 360. Cells 1 to 3). This cell divides by mitosis (Cell No. 2 in Fig. 360) to form the **early** type of **macroblast** [1]—still also without, or only just beginning to acquire, hæmoglobin in its cytoplasm (Nos. 4 to 12). The macroblast is still capable of active mitotic division, especially in its early stages (No. 6); but, as the **late macroblast,** it acquires hæmoglobin and its nucleus becomes smaller and more condensed, it loses this power of division and matures as an individual cell to become the normoblast (Nos. 15, 16 and 17).

The **normoblast** is a cell of from 10μ to 7μ in diameter, *i.e.*, progressively diminishing to about the size of the mature red corpuscle itself. Its cytoplasm is now almost or even completely hæmoglobinised, and its nucleus becomes smaller and more condensed, and, when stained, resembles "a drop of ink." The nucleus, often after a preliminary fragmentation, then disappears, whether by solution within the corpuscle or by extrusion, is not yet fully determined. At this stage, the cytoplasm contains a copious **reticulum** demonstrable by supravital staining with cresyl-blue, and persisting for some time after the

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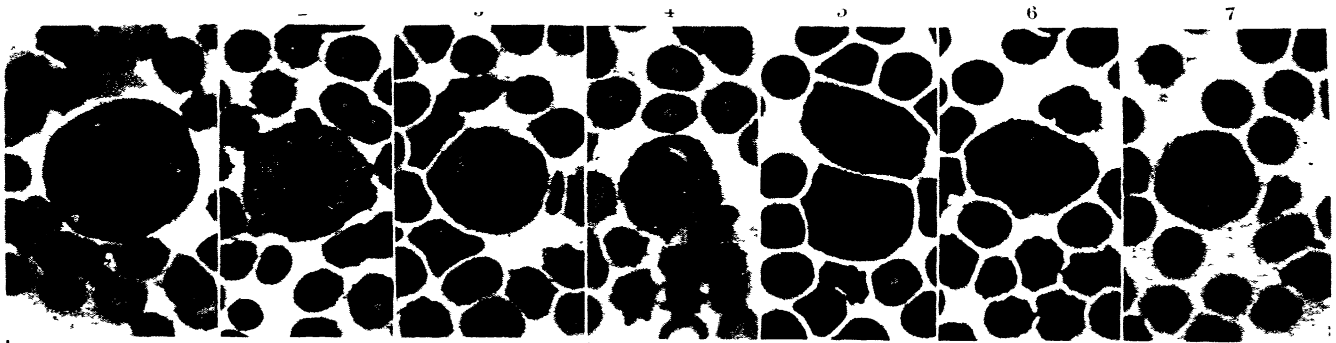
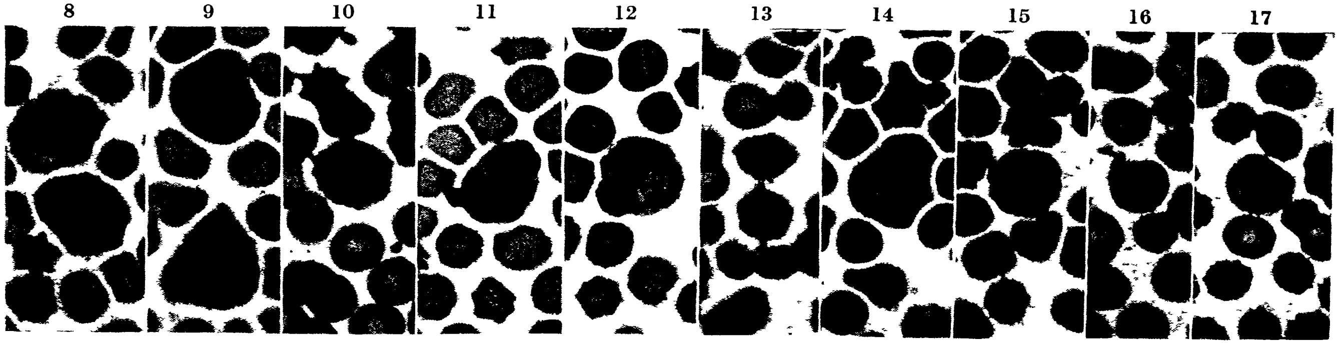
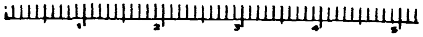
[1] We prefer to use the word "**erythroblast**" as the **generic term** to include **all the nucleated cells** of the red-corpuscle series: and the terms "**macroblast, early** and **late,**" rather than "erythroblast, early and late," for the intermediate cells of the nucleated series. In order to avoid confusion, and because we have recommended the textbook on hæmatology, "Disorders of the Blood," by Whitby and Britton, we ask our readers to note that we employ the terms "macroblast, early and late," as synonymous with the "erythroblast, early and late," of these authors. The earlier large forms of macroblast or "intermediate erythroblast" were formerly included in the category of "megaloblast," and allowance must therefore also be made for the technical variations in the terminology of these cells which readers will encounter in the literature of the subject.



(1 to 3) Non-hæmoglobinised megaloblasts. (4 to 12) Early non-hæmoglobinised macroblasts (or early intermediate erythroblasts) developing into late macroblasts (or late intermediate erythroblasts) . . . . .



(13 to 17) becoming fully hæmoglobinised normoblasts.



(Each mm. division of this scale is approximately equivalent to 1μ.)

FIG. 360. *Erythropoiesis.* Development of the Red-cell Series.

Series of microphotographs made from a single Leishman-stained film of blood aspirated from a subdural hæmatoma (p. 974 *et seq.*), in which these nucleated red cells were present in large numbers (an unusual finding, but one giving a very complete illustrative developmental series). The largest cell (No. 1), a megaloblast with intensely blue-staining cytoplasm, measured 19μ in total diameter, and its nucleus 12μ. The series showed little or no hæmoglobin until cells Nos 9 and 10 : the cytoplasm of Nos. 5 to 8 being pale blue. Cells Nos. 15 to 17 were fully hæmoglobinised normoblasts, which are still slightly larger than the numerous non-nucleated fully developed erythrocytes, most of which, in this particular case, are 6·5μ to 7·5μ in diameter (the normal size being 7 to 8μ). The magnification is approximately × 1,000, and therefore 1 millimetre on the accompanying scale is equivalent to 1μ in the original blood-film.

disappearance of the nucleus, and thus constituting the reticulocyte (Plate XIV, facing this page).

The **reticulocyte** is often but little larger than, or perhaps now equal in size to, the **mature red corpuscle** or **erythrocyte** itself.

As full descriptions of the red corpuscles are included in textbooks of Normal Histology and Hæmatology, reference to only a few points need be made here. In the healthy adult male, the red corpuscles or erythrocytes number about five-and-a-half to six millions per c.mm., and about half-a-million less per c.mm. in the female. This number is increased in plethora, erythræmia or polycythæmia rubra, and diminished in anæmia or oligocythæmia rubra. In estimating the value of observations upon the number of red corpuscles present, possible temporary variations in the amount of the fluid constituents of the blood must be borne in mind.

In some pathological conditions, *e.g.*, the anæmias, the normal tendency to the formation of rouleaux may be only slight, or even entirely absent.

Anisocytosis or **variation in the size** of the erythrocytes occurs in many diseased conditions. Abnormally large corpuscles are known as **macrocytes** (or megalocytes), those which are diminished in size being termed **microcytes,** and those of normal dimensions, **normocytes.** The thickness of the normal erythrocyte is about 2μ, *i.e.*, approximately one quarter of its diameter (Figs. 357–8, p. 586). Red corpuscles which still retain their nuclei are known as erythroblasts,[1] and these in turn are classified respectively as megaloblasts, macroblasts, normoblasts and microblasts, short descriptions of which are given in the above introductory note. Certain red corpuscles of exceptionally large size (*e.g.*, over 20μ in diameter), and found especially in uncontrolled Addisonian or "pernicious" anæmia, are known as gigantocytes, or, if still nucleated, as gigantoblasts. Slighter degrees of anisocytosis occur in a great variety of conditions, including almost all cases of even mild degrees of anæmia or of septic infection, in which there is disturbance of the hæmopoietic functions of the bone-marrow ; and it is still more pronounced in the severer grades of such disturbances of blood-formation.

Similarly, in certain conditions in which the equipoise of the hæmopoietic functions of the marrow is more seriously disturbed, *e.g.*, after hæmorrhage, in the severer grades of anæmia and in the leukæmias, nucleated red cells may pass out into the blood and, when this occurs in large numbers, the blood-condition is known as **erythroblastæmia** (p. 638). This may occur also, though usually only in slight degree, as an accompaniment of leucocytosis, especially if the latter is excessive. The passage of nucleated red cells into the circulating blood takes place much more readily in children. In some cases of anæmia, the nucleated red corpuscles become specially numerous in the peripheral circulation just before death ; and, in several such cases observed by the authors, this phenomenon appears to have been increased by the administration of large saline transfusions—perhaps by the mechanical washing-out of these cells from the bone-marrow.

Reticulocytes, as already defined above, are slightly immature corpuscles, and represent normoblasts from which the nuclei have recently disappeared. In health, about 1 in 500 corpuscles still show reticulation, but in pathological

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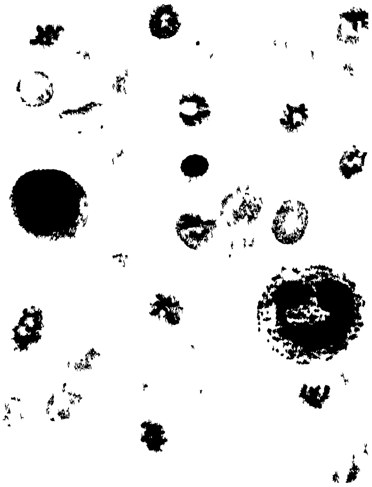
[1] *See* footnote on p. 592.

PLATE XIV, p 594.



Blood-Film showing numerous Reticulocytes stained supra-vitally with brilliant cresyl-blue followed by Leishman's stain. × 500
a.a.a. Reticulocytes.

disappearance of the nucleus, and thus constituting the reticulocyte (Plate XIV, facing this page).

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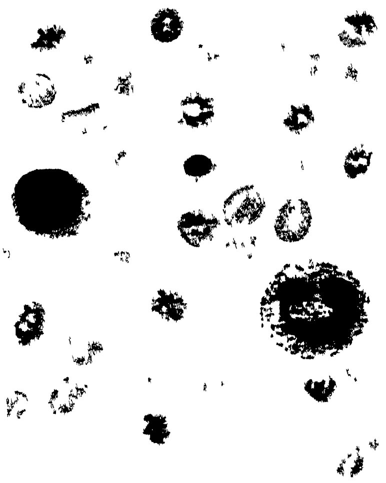

Blood-Film showing numerous Reticulocytes stained supra-vitally with ***brilliant*** *cresyl-blue followed by Leishman's stain.* × **500**
*a.a.a.*Reticulocytes.

conditions such as acholuric jaundice or Addisonian or "pernicious" anæmia under treatment, the number may reach 20 per cent., or sometimes even higher proportions, of the red corpuscles (Plate XIV, facing p. 594).

Hæmoglobinised megaloblasts. These, as explained in the foregoing introductory paragraphs, occur in the bone-marrow and circulating blood in untreated Addisonian or " pernicious " anæmia, and occasionally in the anæmias produced by certain intestinal parasites, *e.g.*, *Diphyllobothrium latum* (*Dibrothriocephalus latus*) and *Ankylostoma duodenale.* It may be noted here that, though hæmoglobinised megaloblasts are rarely found in the blood except in the above conditions, they, and also the primitive but hæmoglobinised macroblasts derived from them, are by no means of uncommon occurrence in the bone-marrow itself in many diseases, not only in children—in whom they are comparatively common—but also in adults. One of the authors has repeatedly found them in the bone-marrow in such conditions as acute septic diseases, typhoid fever, malignant disease, exophthalmic goitre, etc., in the adult ; and in diphtheria and many other acute and chronic diseases in children.

Degenerative phenomena are common in red corpuscles (Plates XV and XVIII, facing pp. 596 and 650). The more important of these may be summarised as follows :—

Poikilocytosis. In some anæmias the red corpuscles are distorted in shape, and are then known as **poikilocytes** (Plate XVIII, Figs. 1 and 4). **Crenation,** or the artificial production of knob-like projections on their surface, due to changes in osmotic pressure, must, of course, be distinguished from this condition.

Spherocytosis. In acholuric jaundice, the red corpuscles show considerable alteration from the normal in size and shape, their transverse diameter being diminished, and the corpuscles being more spherical or thicker, and hence they appear smaller and darker than normal with transmitted light. The corpuscular volume is, however, practically unaltered, as the two changes tend to neutralise each other (p. 586 and Figs. 357 and 358), the thickness becoming perhaps as much as half the diameter. Spherocytosis, together with increasing fragility, gradually supervenes **in drawn blood** which has been stored for purposes of **transfusion,** but its therapeutic properties and value apparently do not become seriously impaired during the first three weeks of efficient storage.

Colour-changes in the Erythrocytes. These alterations are most commonly of the nature either of increase, or, more usually, of diminution, in the amount of the contained hæmoglobin. When viewed flat, the normal red corpuscle, owing to its bi-concave shape, is seen to have a slightly paler central part, which represents the correspondingly thinner layer of hæmoglobin in this area. When the hæmoglobin contained within the erythrocytes is diminished from any cause, *e.g.*, in anæmias, this central pale area becomes exaggerated. In severe cases, it may be colourless and transparent, and the hæmoglobin may appear as a narrow pale-red ring around it at the periphery of the corpuscle. In Addisonian or " pernicious " anæmia (p. 646), on the other hand, although the total amount of the hæmoglobin in the blood as a whole may be, and usually is, much reduced, yet the amount *per individual corpuscle* is on the average increased and the colour-index is therefore above unity. In this connection it must be borne in mind that, though greatly diminished in numbers, many of the corpuscles are individually of larger size than normal. The actual concentration of hæmoglobin, and consequently the staining-capacity of the individual corpuscles, varies greatly, many often being darker but others lighter than normal in colour, both in stained and in unstained films.

Polychromasia, Polychromatophilia or Diffuse Basiphilia. In some conditions, red corpuscles, when stained with methylene-blue and eosin (or some such combination of stains, as in Leishman's, Jenner's or Wright's modifications of the Romanowsky method), do not show the usual bright-red coloration of their disks with the acid stain ; but, on the contrary, exhibit a varying admixture of blue-staining (Plate XVIII, Fig. 1, p. 650). This is a sign of immaturity, the red corpuscles being rapidly and imperfectly formed in the bone-marrow, and finding their way into the general circulation before they have developed their full complement of hæmoglobin (Fig. 360, p. 593). Reticulocytes frequently show varying degrees of polychromasia, and hence the phenomenon is often pronounced in conditions in which these immature corpuscles are increased in number.

Punctate Basiphilia or Granular Degeneration. In certain conditions, *e.g.*, in malaria, in untreated Addisonian and allied anæmias, and in severe secondary anæmias such as those produced by chronic lead-poisoning, some of the corpuscles show the presence of numerous minute blue-staining points (Plate XVIII, Fig. 1). The exact nature of these has not yet been ascertained, some regarding them as the remains of the fragmented nucleus, whilst others believe them to be due to degenerative changes in the cyto-reticulum, and a few hæmatologists even regard them as artefacts. Somewhat analogous points or dots (Schüffner's and Maurer's dots) are of frequent occurrence in the invaded corpuscles in malaria, especially in the benign tertian form of the disease. These, however, stain bright red ; whereas, often in the same films, the blue-stained points of the punctate basiphilia may be seen in some of the degenerated, but uninfested, corpuscles.

Colour-changes in the red corpuscles may be due also to the action of certain **poisons.** Carbon monoxide (p. 1186) and sulphuretted hydrogen form definite chemical compounds with the hæmoglobin. Poisons absorbed from the alimentary canal may similarly form methæmoglobin and sulphhæmoglobin, and may give rise to a peculiar tinting of the skin and mucous membranes known as **enterogenous cyanosis** : or poisonous substances may be absorbed through the skin or respiratory tract, as in the instance of trinitrotoluene ("T.N.T."), tetryl ("C.E.") and similar compounds used as explosives. In some cases the altered pigment may be retained *within* the red corpuscles, the change in colour being then due mainly to the inability of the new compound to take up sufficient oxygen. In other instances, if hæmolysis or destruction of the red corpuscles also supervenes, the pigment may be freed into the plasma and be excreted in the urine—met- or sulph-hæmoglobinæmia and -hæmoglobinuria respectively, changes which are also induced by such drugs as trional, sulphonal and the sulphonamide-series of compounds.

THE WHITE BLOOD-CORPUSCLES OR LEUCOCYTES

In fresh unstained preparations, the leucocytes appear as clear, colourless, refractile cells, the smaller varieties of which are 7 or 8μ in diameter, *i.e.*, about the size of the red corpuscles, whilst the diameter of the larger types may be half as large again as, or twice that of, the erythrocytes, or more. If

DESCRIPTION OF FIGURE 200, PLATE XV

PLATE XV

FIG. 1. *Film of Normal Blood* (stained with hæmatin and eosin). The red blood-corpuscles are regular in outline and in size.
a.a. Polymorphonuclear leucocytes.
b. Eosinophil leucocyte.
c. Small lymphocyte.
d. Large hyaline leucocyte or monocyte.
e. Blood-platelets. × 500

FIG. 2. *Blood-Film from a case of Neutrophil Polymorphonuclear Leucocytosis* (stained with eosin and methylene-blue).
a.a. Polymorphonuclear leucocytes.
b. Medium-sized lymphocyte.
The red corpuscles do not exhibit any obvious changes. × 500

FIG. 3. *Blood-Film from a case of Myeloid Leukæmia* (stained with Jenner's stain).
a.a. Mature polymorphonuclear neutrophil leucocytes.
b.b. Immature polymorphonuclear neutrophil leucocytes.
c.c. Intermediate neutrophil myelocytes.
d.d. Small neutrophil myelocytes.
e.e. Large neutrophil myelocytes.
f. Non-granular mononuclear cell, possibly a myeloblast, promyelocyte or parent-cell of the granular myelocyte.
g.g. Eosinophil myelocytes.
h.h. Basiphil cells.
i. Small lymphocyte.
k. Large lymphocyte.
l.l. Normoblasts. × 500

FIG. 4. *Blood-Film from a case of Lymphatic Leukæmia* (stained with Leishman's stain).
a. Polymorphonuclear leucocyte.
b.b. Small
b.b′. Medium-sized } lymphocyte-like cells. (p. 631 *et seq.*)
b.b″. Large
c. Normoblast.
c′. Normoblast with fragmented nucleus. × 580

PLATE XV

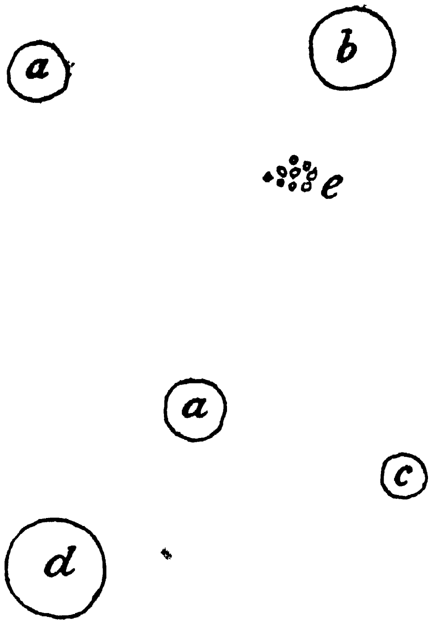

FIG. 1.

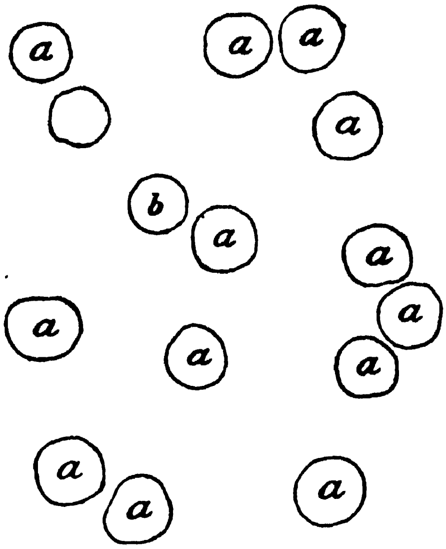

FIG. 2.

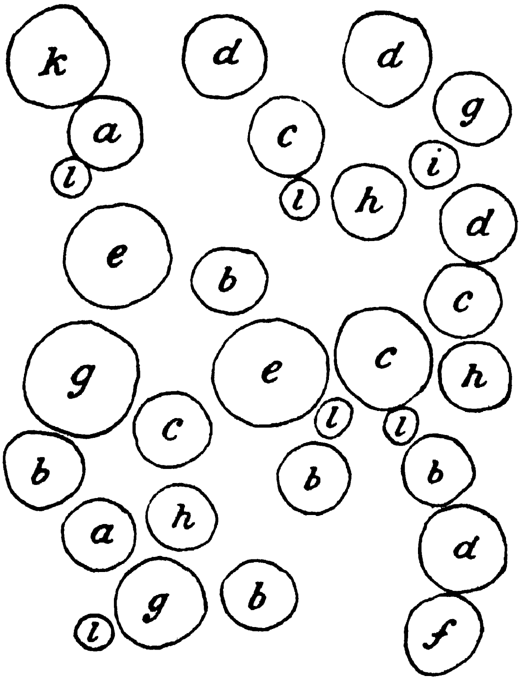

FIG. 3.

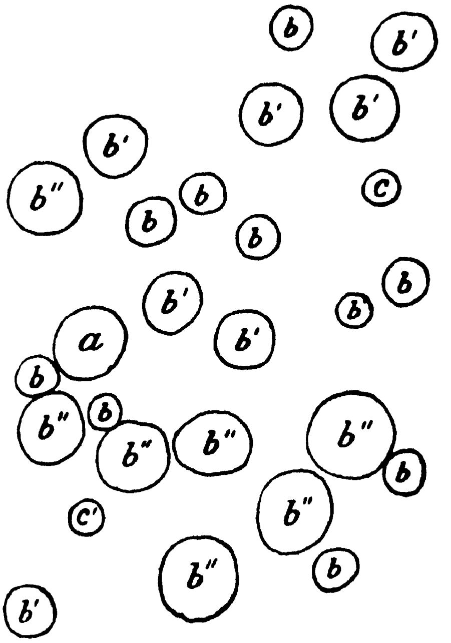

FIG. 4.

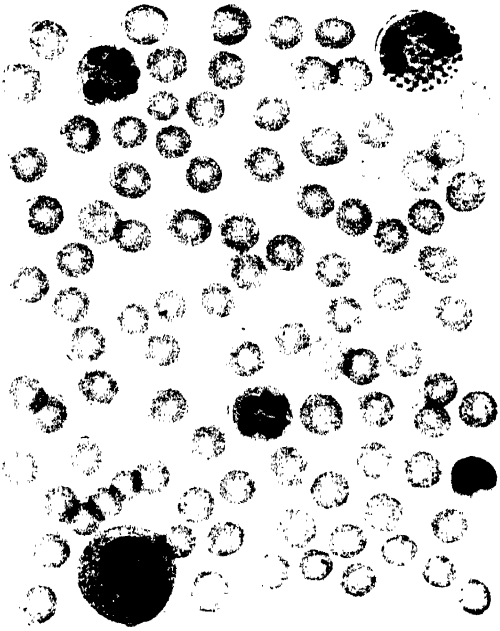

FIG. 1. × 500

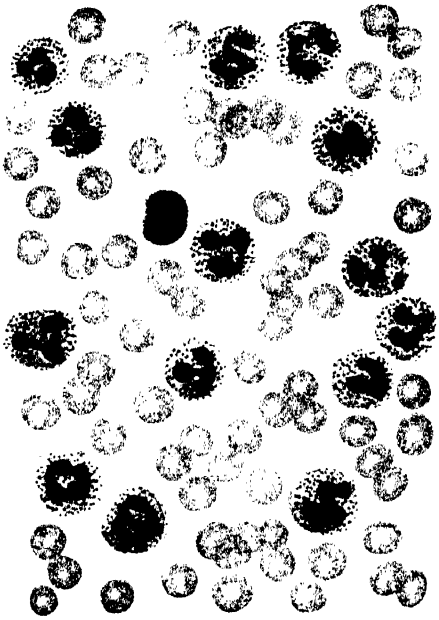

FIG. 2. × 500

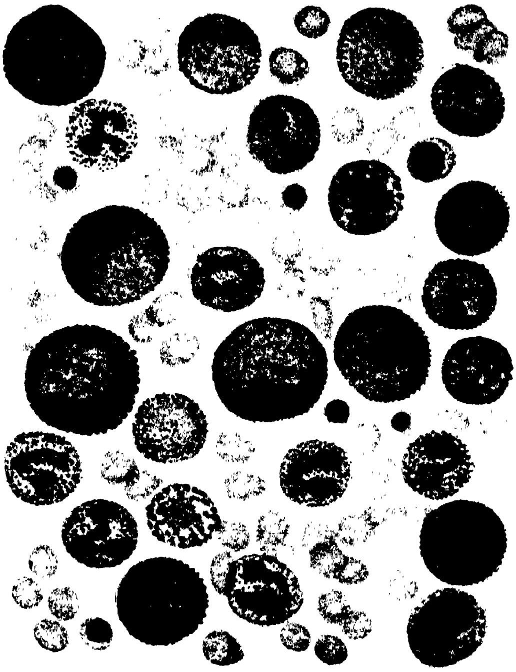

FIG. 3. × 500

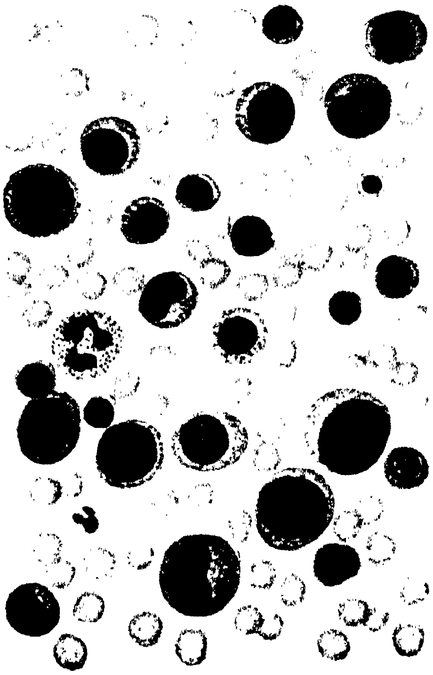

FIG. 4. × 500

examined under suitable conditions on the warm stage, the polymorphonuclear and large mononuclear cells or monocytes are seen to be actively amœboid, whilst the smaller lymphocytes, when observed in a suitable environment, are also distinctly motile (pp. 600–600A). The fine granules of the polymorph cells, and the coarser granules of the eosinophils, are distinctly visible as highly refractile particles in the cytoplasm, with, especially in the latter variety of cell, a pale-greenish tinge due to refraction. "Vacuoles," or clear rounded spaces filled with liquid, are often visible in the cytoplasm, particularly if the cells have been ingesting foreign particles. In the case of the large mononuclear cells, the cytoplasm has a delicately reticulated appearance. When observed on the warm stage, fine streaming, and also to-and-fro dancing, movements, may be observed in the cytoplasm of the polymorphonuclear leucocytes and monocytes, especially when these cells are exhibiting phagocytic activities, as, for example, in the freshly drawn blood of a patient with malaria. In such a specimen, all phases of the phagocytic process may be watched under the microscope, a single monocyte often being seen to ingest several malarial parasites in succession. Other rhythmic movements may also be noted, for example, a species of pulsatile motion in the walls of the vacuoles, if these be present. It will also be observed that the nucleus of such a cell, or of a polymorphonuclear leucocyte, during activity, does not remain motionless and stationary; but may, from time to time, be seen actively to change its shape and relative position within the cytoplasm.

Emigration of leucocytes through the vessel-wall, and their active migration through the tissues, may be observed in suitably arranged specimens, *e.g.*, in fresh, moist preparations of frog's mesentery. The polymorph cells are usually the first to leave the vessels, the monocytes passing out later. In this connection it may be stated that the small lymphocytes are also amœboid, and can take part in the process of emigration (p. 600), though less actively than the foregoing varieties. These phenomena are described in the Chapter on Inflammation (p. 32 *et seq.*).

The presence of **glycogen** in the cytoplasm of neutrophil polymorphonuclear leucocytes in certain pathological conditions, especially those characterised by neutrophil leucocytosis, is described on p. 207.

Varieties and Relative Numbers of the White Cells [1]

In a cubic millimetre of blood drawn from the peripheral circulation, under normal circumstances, there are present about 8,000 white cells. Variations occur in this number both in health and in disease—a subject to which special reference is made in the section on Leucocytosis (p. 617).

In the following table (p. 598), are enumerated the varieties of leucocytes found in the peripheral blood of normal individuals, together with their average relative or percentage numbers and their absolute numbers per c.mm., calculated from 8,000 as the average total leucocytes per c.mm.

It will be seen from the figures in the table that, in considering the significance of pathological variations in a **relative percentage leucocyte-count,** the elative figures must be carefully compared with those of the **total leucocyte-**

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[1] *See also* Section on "The Cells of Acute Inflammatory Exudates," p. 26 *et seq.*

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[1] *See also* Section on "The Cells of Acute Inflammatory Exudates," p. 26 *et seq.*

	VARIETY OF LEUCOCYTE	RELATIVE NUMBERS per cent.	ABSOLUTE NUMBERS per c.mm. (taking 8,000 as Average Total).
i.	Finely-Granular Neutrophil POLYMORPHONUCLEAR Leucocytes .	60 to 70	4,800 to 5,600
ii.	Coarsely-Granular EOSINOPHIL Leucocytes .	1 to 4*	80 to 320
iii.	BASIPHIL Granular CELLS ("mast-cells") .	under ½	under 40
iv.	LYMPHOCYTES (Large and Small) . .	25 to 35	2,000 to 2,800
v.	Large Mononuclear HYALINE Cells or MONOCYTES	3 to 6	240 to 480

* With regard to the number of Eosinophils, *see* p. 599 opposite.

count; and, if necessary, the **absolute numbers** of each variety of leucocyte per c.mm. should be calculated—otherwise an erroneous impression may be given by the figure of the relative percentage-count alone.

A detailed description of the various forms of leucocytes is given in the Chapter on Inflammation (pp. 26 *et seq.*), but it is convenient to repeat this description here. Reference should also be made to Plates I, II, III, IV, V, XIII, XIV, XV, and XVIII.

Neutrophil Polymorphonuclear Leucocytes (*cf.* pp. 26 and 620). These leucocytes are the most numerous variety in the blood, in which they constitute about 60 to 70 per cent. of the total leucocytes. They have a nucleus which is divided into segments or lobes, the segments, in the fully mature cell, being connected by means of delicate filaments of chromatin. The number or complexity of these lobes has been observed to be **increased** in some toxic conditions [1]; but, where there is stimulation of the leucoblastic functions of the bone-marrow and the passage into the circulation of immature forms, these show **decreased** complexity of the nucleus and a smaller number of lobes, or even some entirely non-lobulated forms—forms still at the stages between the neutrophil myelocyte and the polymorphonuclear leucocyte.[1] Carnegie Dickson has noted great exaggeration in the complexity of the polymorph nucleus under the experimental action of snake-venom, whilst thyroid-extract also appears to have a certain action in this direction. The cytoplasm contains irregularly scattered, fine granules which stain faintly with eosin, but are usually described as "neutrophil." As has already been noted, these leucocytes are actively amœboid and phagocytic. In the process of phagocytosis they are concerned especially with the destruction of bacteria; and, from the fact that they are smaller than the other actively phagocytic cells of the blood, viz., the large mononuclear cells or monocytes, they were called **microphages** by Metchnikoff. In the majority of bacterial infections, these cells are increased in number, the condition being termed a **polymorphonuclear leucocytosis,** or—from the fact that it is usually produced by more or less acute bacterial infections—**inflammatory leucocytosis** or **leucocytosis** proper. Variations in the number, size, regularity and staining-reactions of the cytoplasmic granules occur in certain pathological conditions They may be scanty and small in cases where the cells are being rapidly produced, *e.g.*, in excessive or prolonged polymorph leucocytosis or in myelogenous leukæmia (p. 626).

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[1] *See* p. 620, for a note on these changes in leucocytosis, the Arneth-count, etc.

Coarsely Granular Eosinophils (*cf.* p. 26) are usually stated to constitute from 1 to 3 or even 4 per cent. of the white cells of normal blood, but the count even in health is variable. The proportion of these cells is increased when there is any tendency to the so-called " allergic " state, and thus some otherwise apparently normal persons may show a minor increase in the number of eosinophils present. In the experience of the authors, the healthy average is about 1 to 1½ per cent. When stained with eosin, they show in their cytoplasm brilliantly coloured pink granules, which are much larger and more highly refractile than those in the polymorphonuclear leucocytes. The lobed character of the nucleus is not so marked, there are most commonly two lobes, usually somewhat larger than those of the neutrophil nucleus and staining rather less intensely with the basic dyes. Eosinophil cells are fragile, and readily break down, with scattering of their granules. In certain disorders, especially in diseases due to animal parasites, this variety of leucocyte may be greatly increased in number (pp. 362, 391, 399–400, 414–5 and 419).

Basiphils (" mast-cells ") (*cf.* pp. 27, 163 and 623) number about one-half per cent. of the circulating white cells and are characterised by the presence of irregularly scattered, larger and smaller basiphil granules, or granules which show metachromatic staining, and the deeply-staining nucleus being either single or lobed — often trilobed. These cells are more numerous in some pathological disorders, *e.g.*, myeloid leukæmia or leucosis (p. 628). The view that the basiphil leucocytes are degeneration-products of other cells has been proved now, from observations with supravital and other staining-methods, to be incorrect, and the term " mast-cell," which implies degeneration (*see* footnote on p. 623), should therefore be discarded. The recent work of Jorpes [1] and his collaborators in Stockholm (1939) upon the number and distribution of the basiphils—as fixed tissue-cells—in the walls of capillaries and of the non-muscle-containing smaller blood-vessels, and the metachromatic staining of their granules with thionin or toluidin blue, appears to show that these basiphil granules either consist, or are concerned with the production, of the **anticoagulant substance heparin** (p. 162). Jorpes has

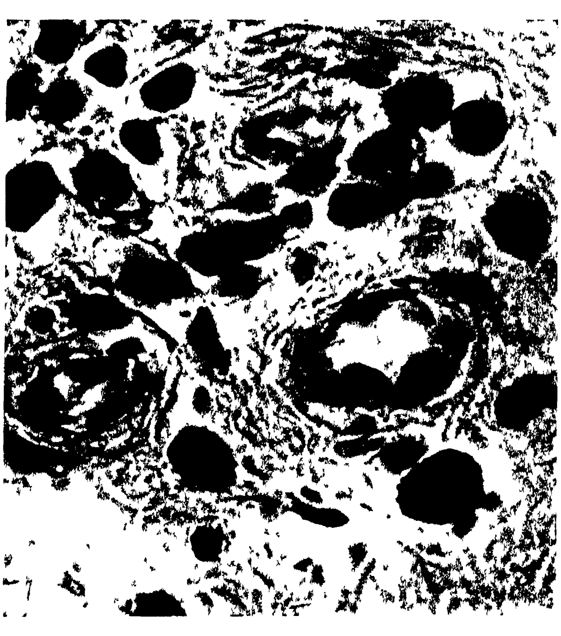

FIG. 360A.—*The basiphil cells in the walls of capillaries,* believed by Jorpes to be concerned in the production of " *heparin.*" × 1000.

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[1] " Heparin: Its Chemistry, Physiology and Application in Medicine," by J. Erik Jorpes, Stockholm, Oxford University Press, 1939.

found that the heparin-content of the various tissues corresponds with the numbers of the **basiphil cells** present in them ; and he suggests that the chemical composition of their granular contents and their distribution in the walls of the small blood-vessels (Fig. 360A) are compatible with his hypothesis that they pour their anticoagulant secretion into the blood-stream or perivascular tissue-juices, and thus maintain the fluidity of the blood and tissue-juices. The small numbers—only between a half and one per cent.—of these basiphils that find their way into the blood-stream may, therefore, be regarded as perhaps only an accidental overflow-phenomenon, the cells being, under normal circumstances, of the nature of fixed-tissue cells rather than blood-cells proper.

The Mononuclear Leucocytes, as they occur in the blood, may be classified thus :—

Lymphocytes (*cf.* pp. 27 and 28). These vary in size. In health, the majority are comparatively small cells—about the size of a red corpuscle or slightly larger—with a relatively large, darkly-staining nucleus, and only a scanty rim of cytoplasm, in which a few small basiphil or, more accurately, " azurophil," granules can usually be seen, either scattered irregularly or situated near the periphery. Others, regarded by most hæmatologists as the more immature cells of the lymphocyte-series, are larger and similar to those described, but have more abundant cytoplasm (the large lymphocytes), all sizes between the typical large, and the typical small, lymphocyte being found. The relative numbers of large and small lymphocytes vary much in individual cases and in different age-groups, but the significance of such variations is still debated, and there is now a tendency to omit the distinction between the so-called " large " and " small " varieties. These together constitute from about 25 to 35 per cent. of the colourless cells of the blood. In many irritative conditions of the lymphadenoid tissues of the body, including that of the intestine, the larger (*i.e.*, more immature [1]) cells of the series, including, it may be, a varying number of lymphoblasts (p. 631), are often increased in the peripheral blood. Lymphocytes are relatively more numerous in children than in the adult, both in health and in disease ; and, with the partial atrophy of the lymphadenoid tissues in old age, they tend to diminish as a senile phenomenon.

From recent experimental evidence obtained from their investigation of the lymphocyte-series by cell-culture, as well as from detailed and prolonged observation of fresh living and stained preparations of lymphocytes, from both normal and pathological sources, Medawar,[1] and also Ebert, Sanders and Florey,[2] are of opinion that the views of Maximow and his follower, Bloom (that small lymphocytes can develop either into larger forms of lymphocyte or into other types of cell such as monocytes, polyblasts, macrophages or fibroblasts) are *not* proved. The observations of Medawar and other Oxford workers confirm the views of Clark, Clark and Rex[3] and others that, *in vivo*, the lymphocytes in the tissue are actively motile cells : " . . . they move with their relatively large compact nucleus in advance and a small cytoplasmic process extending posteriorly. Their behaviour outside the vessels is characterised by alternating periods of rapid migration in a relatively straight course followed by longer periods of inactivity in which they assume a rounded form."[1] The lymphocyte, in these experiments, appears to be very sensitive to lack of oxygen. *No* transformations of lymphocytes into other cells were observed, and *no* attempt at phagocytosis was noted in lymphocytes, although they were actively motile.[2]

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[1] " Observations on Lymphocytes in Tissue Culture," by J. Medawar, Oxford, *Brit. Jour. of Exper. Path.*, 1940, **21**, 205.

[2] " Observations on Lymphocytes in Chambers in the Rabbit's Ear," by R. H. Ebert, A. G. Sanders and H. W. Florey, Oxford, *ibid.*, p. 212.

[3] E. R. Clark, E. L. Clark and R. O. Rex. *Amer. Jour. of Anat.*, 1936, **59**, 123.

The functions and ultimate fate of the lymphocytes are still but little understood. In an animal such as the dog, it is estimated that some 200,000,000 lymphocytes pass out from the thoracic duct into the blood-stream every hour—and yet, except for certain rhythmic fluctuations during the day, the lymphocytic blood-content remains practically constant. It is stated by Yoffrey and Drinker (1939) that only one in thirty of these lymphocytes finds it way back into the lymphatic capillaries. What becomes of the other twenty-nine remains a mystery still to be solved.[3]

Monocytes, Large Mononuclear Cells or **Hyaline Leucocytes** (*cf.* p. 27), are present in small numbers in the circulating blood, but are more abundant in certain pathological states, *e.g.*, malaria. In their general characters, they resemble the large lymphocytes, and it is often very difficult to draw any absolute morphological distinction between them. They are generally described as having an ovoid or kidney-shaped nucleus which stains less intensely than that of the lymphocytes, and cytoplasm which is devoid of granules. Certain observers hold that transition-forms between the lymphocytes, small and large, and these hyaline cells can be seen in the blood, and that the one is derived from the other. This, however, does not appear to be in accord with findings obtained by cell-culture, and Israëls (p. 606) is of opinion that they are distinct from one another. In malaria, where there is a great increase of the " hyaline " leucocytes, the ordinary lymphocytes are not, in all instances, proportionally increased ; and similarly in other cases, where the small lymphocytes are greatly increased in number, there need not be any increase in these large monocytes. This would certainly suggest that the two are distinct from one another. It is, we think, highly probable that many of these large monocytes originate from vascular, lymphatic, and serous endothelium, and from cells of the reticulo-endothelial system. They show active amœboid movement on the warm stage, and are able to pass out of the vessels in virtue of this property. They are actively phagocytic, especially against other **cells** or the degeneration-products of these, and thus constitute an important variety of **macrophage.**

Immature and abnormal forms of white cells—such as myelocytes and

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[1] Quoted from Clark *et al.* (1936) by Ebert *et al.*, *loc. cit.*, p. 212.

[2] *Loc cit.*, p. 217.

[3] " The Mystery of the Vanishing Lymphocyte," leading article, *Brit. Med. Jour.* (1940), ii, 873. This article quotes the observations of Yoffrey and Drinker, E. R. and E. L. Clark, W. H. Lewis, Sanders and Florey, and J. Medawar (to some of which we have referred above) all of which appear to show that the lymphocyte does *not* change or develop into any other type of cell. What does become of them calls for further investigation. The writer of this leader cautiously adds that : " Important though these negative conclusions are, they do not finally dispose of the hæmopoietic possibilities of the lymphocyte, for it may be that lymphocytes require to be activated by some agency within the environment of the bone marrow before they can undergo differentiation."

yeloblasts, lymphoblasts and monoblasts—occurring in pathological blood will discussed after the origins of the various blood-cells have been described.

BLOOD-PLATES OR PLATELETS

The exact nature of these bodies is only beginning to be understood. They e small spherical, ovoid or somewhat irregular, extremely adhesive structures, out 2 or 3μ in diameter, though larger forms are not uncommon. They do t stain well with the ordinary dyes, and are seen best in fresh-wet "supra-tally stained" preparations or in dried films which have been rapidly ade, and fixed and stained by some modification of the Romanowsky method, g., Leishman's or Jenner's stain. When so prepared, they are seen to consist a clearer, homogeneous peripheral part, with a darker, sometimes rather anular, reddish or violet centre. They are said to be composed mainly of cleoproteins. Their origin has in the past been much debated, some holding at they were of the nature of extrusions from the erythrocytes (Ewing, aximow, Klebs, Arnold and others); whilst some authorities believed that ey were derived from the nuclei of leucocytes. Others again, with whom agree, from a study of very carefully stained preparations, believe them to produced from the cytoplasm of the mononucleated giant-cells or **gakaryocytes** of the marrow (Fig. 361), from the periphery of which they ak off (Homer Wright). Occasionally, larger fragments of the cytoplasm of se cells are freed and are recognisable as such in blood-films containing them. od-platelets play a very important part in the **formation of thrombi,** lecting around, and adhering with great readiness to, any foreign bodies the blood-stream, or to injured areas on the walls of the blood-vessels or rt (pp. 161 and 163–5); they are also concerned with the **retraction** or **inking of blood-clot**; and they are the chief components of **vegetations** on heart-valves, and, owing to these properties, are sometimes termed **mbocytes**. They probably contain the thromboplastin (thrombokinase)

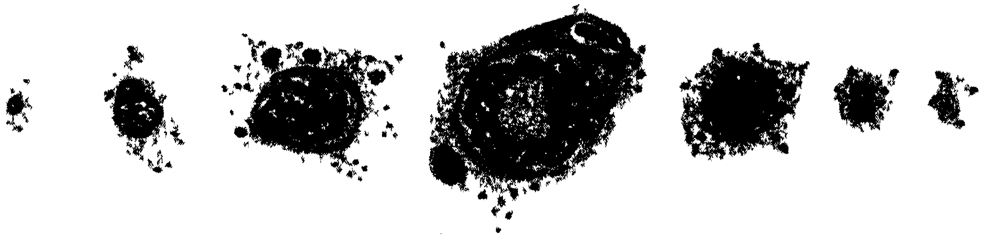

FIG. 361 Megakaryocyte from bone marrow of a healthy rabbit Series of consecutive sections through cytoplasm and the large single composite nucleus. From the periphery of these cells are formed the blood-platelets. The megakaryocytes are also often actively phagocytic, especially to cells of the granulocyte-series, both myelocytes and polymorphs. (Modified from original coloured Plate V of Carnegie Dickson's "The Bone Marrow," 1908) × 600.

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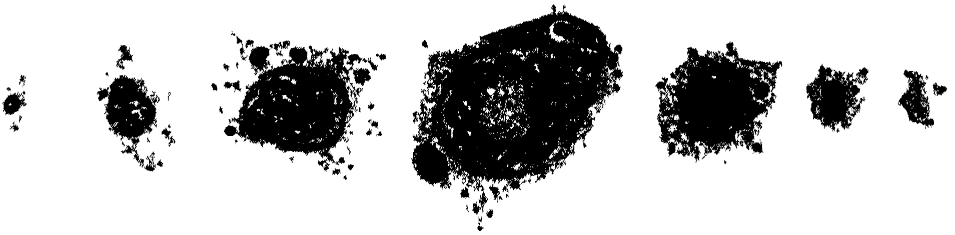

FIG. 361. Megakaryocyte from bone-marrow of a healthy rabbit. Series of consecutive sections through cytoplasm and the large single composite nucleus. From the periphery of these cells are formed the blood-platelets. The megakaryocytes are also often actively phagocytic, especially to cells of the granulocyte-series, both myelocytes and polymorphs. (Modified from original coloured Plate V of Carnegie Dickson's "The Bone-Marrow," 1908.) × 600.

which, in the presence of calcium salts, converts prothrombin into thrombin or fibrin-ferment (p. 161).

The determination of their precise number in the blood is often a matter of some difficulty, but it is probable that, in health, they vary between 200,000 and 500,000, the average normal number being about 250,000 per c.mm. Pathologically, though the recorded results are somewhat contradictory, they appear to be **increased in numbers** after hæmorrhage, in pneumonia, in the earlier stages of myeloid leukæmia, in polycythæmia vera and in many conditions of anæmia. They are generally much increased in numbers after the intravenous injection of horse-serum (either " normal " horse-serum or that containing specific anti-substances) and often also following human-blood transfusion. They are increased after splenectomy (p. 700)—the spleen being concerned in their destruction as one of its special functions (p. 689)—but are diminished in number in typhoid and many other acute fevers, in purpura, hæmophilia and malaria : and in severe intoxications, including poisoning with benzol : and also after undue exposure to X-rays and radium. The increase may favour intravascular clotting of the blood ; whilst, on the other hand, reduction in the numbers or activity of the **megakaryocytes** or mononucleated giant-cells of the marrow will result in a **diminution** in the number of the platelets and will therefore lead to the production of the opposite effect, namely a tendency to the occurrence of capillary hæmorrhages such as are seen in thrombocytopenic purpura (pp. 668–9). On the analogy of the **failure**, in Addisonian anæmia, of the erythroblastic series of cells **to mature,** and similarly, in agranulocytosis, of the leucoblastic series to do so, it has been suggested that thrombocytopenia may be due to failure of the megakaryocytes to produce properly mature platelets ; whilst on the other hand the production of **over-resistant platelets** which do not sufficiently readily break down to form thromboplastin will lead to a failure in their functions as thrombocytes. The subject of " essential thrombocytopenia " or serious diminution or absence of platelets is described on p. 669.

SECTION III

THE BLOOD-FORMING TISSUES

ORIGIN AND FORMATION OF BLOOD-CELLS

In the formation of the **monocytes** of the blood the probable part played by the endothelial cells lining vascular channels, lymphatics and serous surfaces, and by the cells of the reticulo-endothelial system throughout the body, is discussed in the Chapter on Inflammation (pp. 30–1), and also under Meningitis (p. 984 *et seq.*).

Apart from these monocytes, however, in extra-uterine life, the majority of the formed elements of the blood originate in the bone-marrow, as well as in the lymph-nodes and the adenoid tissue of the spleen, intestine, omentum, etc., which are thus also important hæmopoietic tissues. A short description of the physiology and pathology of these may therefore be of value at this point.

I. LYMPHOID TISSUE OF LYMPH-NODES, SPLEEN, INTESTINE, OMENTUM, ETC.

The histology of lymphoid tissue is sufficiently described in standard text-books on Histology and a brief résumé will, therefore, suffice for our purpose. Lymphoid tissue consists of an adenoid reticulum, made up partly of the branching and interlacing processes of its cells and partly of formed connective-tissue fibrils. In the interstices of this reticulum, which is richly supplied with blood-vessels, are situated the closely-packed lymphoid cells—mostly **small lymphocytes** with scanty cytoplasm and relatively large, darkly-staining nuclei. These cells are especially numerous in the immediate vicinity of the " germ-centres "—collections of cells of **larger** and younger type and possessing pale nuclei, probably cells belonging originally to the reticulo-endothelial system which have become differentiated and have taken on lymphogenic function. Such lymphoid tissue is present in the lymph-nodes, in the solitary and aggregated glands of the intestine, in the tonsils, peri-bronchial lymphoid tissue, Malpighian bodies of the spleen, and in the omentum and mesentery, and to some extent in the bone-marrow. It is found also in the thymus gland before the occurrence of its involution.

II. BONE-MARROW [1]

As detailed descriptions of the structure and cytology of the normal marrow are now given in text-books of histology and hæmatology, only brief reference to them need be made here. Autolytic changes supervene rapidly after death, and post-mortem material must, therefore, be examined with as little delay as possible. The most satisfactory findings, however, are those obtained from the examination of biopsy specimens.

Biopsy-Examination of the Bone-Marrow by Puncture and Trephine. The examination of the bone-marrow during life, more especially by **sternal puncture,** is now a recognised procedure of value both clinically and pathologically for the diagnosis and prognosis, as well as for observation of the progress and results of treatment, of disorders of the hæmopoietic system and blood. In such conditions, the blood-picture alone is not always a certain or sufficient guide, and may even be misleading. One of the earlier procedures for obtaining such biopsy-material was the trephining of the upper part of the subcutaneous surface of the tibia [1]; but this method, because of its inconvenience, never came into general use, and, as stated above, the recognised procedure is **sternal puncture.**[2] This is of use especially in diseases in which there is a comparatively uniform alteration, more particularly in the direction of increase, in the hæmopoietic cellular content of the marrow, for example in the leukæmias—especially where an aleukæmic myelosis is suspected (p. 635)—or where a " lymphocytosis " found in the blood in glandular fever has to be differentiated from lymphatic leukæmia or where the condition present is suspected to be agranulocytosis. Defective maturation of the granulocytes in the marrow, with a corresponding reduction in the numbers, or even the complete disappearance, of the granular myelocytes, resulting in deficiency or absence of granulocytes in the circulating blood, can be diagnosed ; as can also any deficiency in the maturation of the earlier cells of the erythroblastic series, for example in Addisonian and other macrocytic anæmias (p. 646).

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[1] Most of this section was based originally upon the pioneer work of one of the authors, W. E. Carnegie Dickson, " The Bone-Marrow : A Cytological Study," Longmans, Green and Co., London, 1908. For more recent detailed information on this subject, we refer our readers to the fourth edition of Whitby and Britton's book on " Disorders of the Blood " (1942).

Where the change in the bone-marrow tends to be **patchy** in distribution, individual biopsy-specimens obtained by sternal puncture and aspiration may not be representative ; or where the marrow is **sclerosed** or has undergone **gelatinous** or **mucinoid degeneration,** the specimen may be scanty, or perhaps no cellular material at all is obtainable for examination. In such circumstances, and particularly if the investigation of the histological architecture of the marrow is desirable, the specimen must be obtained, not by puncture, but by **trephining** the sternum—films and sections of the marrow being then prepared and examined.

Specimens of bone-marrow thus investigated by sternal puncture can usually be classified under the two main types " **erythroblastic** " and " **leucoblastic** " (or " **myeloblastic** "). The ratio of these to one another in individual examples can, with varying degrees of accuracy, be estimated by means of **absolute** and **relative cell-counts** of all the nucleated hæmopoietic cells of both series found in the aspirated (and oxalated) specimen, in the same way as in making a blood-count. The **leuco-erythroblastic** (or **myeloid-erythroblastic) ratio** [3] thus obtained can be compared with the average normal figures

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[1] Probably one of the earliest biopsy-examinations of the bone-marrow was made in the Pathological Department of the Edinburgh Royal Infirmary on January 15th, 1908, at the request of the late George A. Gibson. The specimen was obtained by trephining the subcutaneous surface of the upper part of the tibia of a patient suffering from " splenic anæmia," and was investigated both by film and section and the diagnosis confirmed. For several years previous to that date, it was also a routine procedure to examine as " biopsy-material " the bone-marrow from the portions of rib resected for the treatment of empyema, many of the specimens so obtained showing the reactions characteristic of the acute, subacute and chronic infective conditions producing the empyema.

[2] For details of this procedure and the results obtained by it, see various papers on " The Examination of the Bone-Marrow by Sternal Puncture," by M. S. Arinkin in *Folia hæmatologica*, Leipzig, 1929, **38**, 235 ; M. Salah, of Cairo (whose pattern of puncture-needle is now generally used) in *Jour. Egypt. Med. Assoc.*, 1934, **17**, 10 ; A. F. Zanaty, Cairo and St. Bartholomew's Hospital, *Lancet*, 1937, **ii**, 958 ; M. Hynes, Middlesex Hospital, *Lancet*, 1939, **i**, 1373 ; " La Ponction Sternale : Procédé de Diagnostic Cytologique," by P. Émile-Weil and Suzanne Perlès, Paris, 1938 ; and Whitby and Britton's " Disorders of the Blood," 4th Edition, 1942, 561. Sternal puncture can also be utilised for blood-transfusion in patients in whom, from smallness, collapse, contraction or thrombosis of veins, the usual intravenous route is not available—**intrasternal transfusion** (L. M. Tocantins and J. F. O'Neill, *Surgery, Gynecology and Obstetrics*, Chicago, 1941, **73**, 281).

[3] " Leucoblastic-erythroblastic " or " leuco-erythroblastic ratio " is the more correct term, as " myeloid " means " belonging to the marrow " as a whole.

The Normal Myelogram
with
Suggested Ranges
in
The Differential Cell-Count of the Marrow-Cells
(modified from Martin Hynes [1])

Cells:	Percentages:		
Megaloblasts	0 to 4	**Total Cell-Count** from 25,000 to 100,000 per c.mm. with an average of about 50,000 per c.mm. **Leuco-Erythroblastic Ratio** from 2 to 1 up to 8 to 1 and an average of 4 to 1	
Macroblasts (or Intermediate Erythroblasts)	2 to 7		
Normoblasts	7 to 19		
Monocytes (and Monoblasts)	0 to 5		
Plasma-Cells	0 to 1		
Lymphocytes (and Lymphoblasts)	5 to 20		
Myeloblasts	0 to 2·5		
Promyelocytes	0·5 to 5		
	(Neutrophil)	(Eosinophil)	(Basiphil)
Myelocytes	2 to 8	0 to 1	—
Metamyelocytes [2]	2·5 to 12	0 to 2·5	—
Non-segmented Polymorphs [3]	20 to 40	0 to 2	0 to 1
Segmented Polymorphs [4]	9 to 30	0 to 3	0 to 0·5

[1] "Sternal Puncture," by Martin Hynes, London, *Lancet*, 1939, i, 1373. The figures in the above table must be regarded as *approximate* only. They vary considerably (partly because of the variability of such preparations : and partly on account of differences in nomenclature) from those given by other writers such as Émile-Weil and Suzanne Perlès (*loc. cit.*, p. 32) : or Janet Vaughan (*Practitioner*, 1940, **145**, 351–2).

[2], [3], [4] These, in our own previous editions, we have been accustomed to call "intermediate myelocytes," "immature polymorphs," and "mature polymorphs" or simply "polymorphs," respectively.

given in Hynes' useful table of marrow-cells which (in modified form) we quote, these constituting what may be called the "**myelogram**" of the case.[1] The general cellular character of any individual specimen of bone-marrow can thus be recorded as predominantly leucoblastic (myeloblastic) or predominantly erythroblastic as the case may be ; and, if the latter, whether normoblastic ; early or late macroblastic (early or late erythroblastic) ; or megaloblastic, with, if desired, further refinements which can be deduced from a study of the table. References to certain of the biopsy-findings in diseases are made in the various sections of this chapter dealing with the individual disorders of the blood-forming organs.

The detection of **malignant cells** in sternal-puncture specimens may serve to confirm the suspicion of any invasion of the marrow in malignant disease (p. 730), and such findings are most significant when the cells are present in characteristic groups. Leiv Kreyberg and Erik Poppe,[1] of Oslo, working with parallel series of smears and sections of sternal bone-marrow, obtained positive results in eight out of one hundred patients with malignant tumours—the investigation of sections being found to be the more reliable of the two methods.

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[1] Compare the "*myélogramme,*" normal and pathological, of Émile-Weil (*loc. cit.*), analogous to the corresponding types of "blood-picture" in health and disease. The cytological finding in the case of the spleen is similarly now described as a "splenogram."

Investigation of the **artificial growth of marrow-cells in cell-culture** is a possible method of clearing up certain of the still doubtful problems in the cytogenesis and development of the cells of the bone-marrow. Work in this direction has been carried out by M. C. G. Israëls,[2] (1940), who, elaborating the technique of Osgood and Brownlee [3] (1937), has employed biopsy-material obtained by sternal puncture from patients suffering from one or other of the various types of leukæmia. From the investigation of these he was able to make cell-cultures in which the granulocyte-, lymphocyte- and monocyte-series respectively were the predominating cell, and he concludes that, under the conditions of his experiments, these three groups of cells show characteristic differences from one another, and that forms intermediate between them do **not** occur, and he therefore disagrees with the belief of Maximow and Bloom that the lymphocyte possesses " wide powers of change into other blood cells."

Sternal puncture is useful also for the investigation of the presence of certain **parasites,** for example, those of malaria, kala-azar, and other protozoal infestations; whilst **bacterial cultures from the marrow** ("medulloculture") are often more successful than are the corresponding blood-cultures, for the isolation and identification of streptococci, and typhoid, paratyphoid and other bacteria in infections with these organisms, and are thus sometimes useful in clearing up an otherwise doubtful diagnosis.

VARIETIES OF BONE-MARROW

(Plate XVI and Figs. 362 to 372)

Primitive or Embryonic Marrow. The medullary cavities of the bones are, early in development, filled with a tissue composed of cells, mucoid, mucinoid or " myxomatous " in type, possessing numerous branching and interlacing processes. These are, in histological structure and appearance, similar to the cells found in other " mucoid tissues " in the fœtus ; and, in this situation, they afterwards develop into the reticulo-endothelial cells and adenoid reticulum or framework of the marrow, in the interstices of which appear, about the fourth month of fœtal life or a little earlier, the hæmopoietic cells proper. These cells are themselves probably derived from the reticulo-endothelial cells, and constitute the parent **hæmatoblasts** of some writers. By the proliferation of these cells is formed the next variety of marrow.

Red, Hæmatoblastic or Formative Bone-Marrow proper, in which, except during fœtal, and perhaps early infant, life, when the liver and spleen still retain some of their primitive hæmopoietic functions, are developed **all the red**

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[1] " Tumour Cells in Sternal Bone-Marrow," *Lancet,* 1940, i, 593.

[2] " The Culture *in vitro* of Leucocytes from Human Bone-Marrow," *Jour. Path. and Bact.,* 1940, **50,** 145.

[3] *Jour. Amer. Med. Assoc.,* 1937, **108,** 1793.

DESCRIPTION OF PLATE XVI

PLATE XVI [1]

Naked-Eye Appearance of the Bone-Marrow in Various Acute Diseases

(These illustrations are from the upper portions of the shaft of the femur, except No. 2, which is from the upper part of the humerus)

1. From a case of Acute Lobar Pneumonia accompanied by Leucopenia (male, aged 41), illustrating the practically complete absence of any leucoblastic reaction on the part of the bone-marrow, and accounting for the non-appearance of leucocytosis in this case, the disease progressing rapidly to a fatal termination.

2. From a case of Acute Lobar Pneumonia accompanied by Leucopenia (female, aged 65), showing the same condition as the foregoing specimen, only a trifling amount of congestion being shown in these two sections. Note the very small areas of incomplete leucoblastic transformation. The marrow is fatty practically throughout.

3. From a case of Acute Lobar Pneumonia of five days' duration (male, aged 48), illustrating the earlier stages of Leucoblastic Transformation in acute disease characterised by Polymorphonuclear Leucocytosis. A considerable amount of fat is still present, and the red reaction is seen spreading inwards from the periphery. The cancellated bone has as yet undergone only partial absorption.

4. From a case of Rheumatic Pericarditis of fourteen days' duration (female, aged 14). The condition was accompanied by well-marked Polymorphonuclear Leucocytosis. The Leucoblastic Transformation is passing inwards from the periphery, and the cancellated bone is undergoing absorption.

5. From a case of Septic Peritonitis of three days' duration due to Perforated Gastric Ulcer (female, aged 24). The medullary cavity has not yet had time to enlarge by process of bone-absorption, though the smaller trabeculæ towards the central part have disappeared. The marrow has a diffuse, slightly mottled, dark red appearance due to engorgement of the venous sinuses and capillaries and to a diffuse network of leucoblastic tissue. Note the area of fatty tissue at the lower part of the figure, *i.e.*, the central part of the shaft, where the transformation from yellow to red marrow is last to occur.

6. From a case of Chronic Septicæmia of about a year's duration. Upon the long-continued Leucoblastic Reaction, exhaustion of the tissue had supervened, as evidenced microscopically by the commencement of gelatinous degeneration. The leucoblastic reaction is now being replaced by an erythroblastic one due to the presence of the secondary anæmia caused by the long continuation of the disease, as well as to the exhaustion of the leucoblastic function of the marrow. From the lower part of the longitudinal section the marrow has been removed by washing, in order to demonstrate the absorption of the cancellated bone and partial erosion of the compact bony walls of the medullary cavity. The oblique entrance of the medullary artery is also shown.

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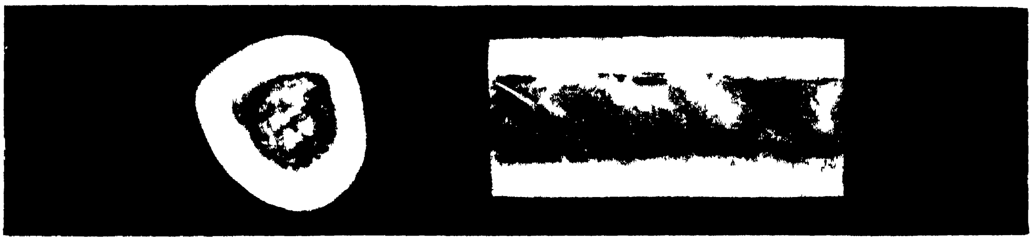
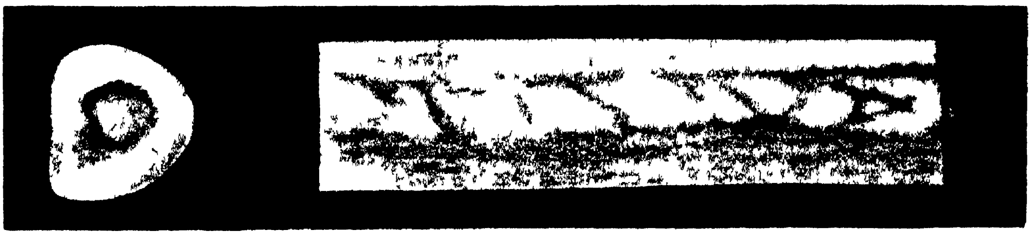
[1] (Reduced from the original coloured Plates VIII, IX and X of Carnegie Dickson's "The Bone Marrow," Longmans, Green and Co., London, 1908.)

PLATE XVI p





corpuscles or erythrocytes, the majority, if not all, of the **granular leucocytes**, and also some of the **non-granular white cells** of the blood.

In the infant and young child, this formative type of marrow is found throughout the interior of the entire osseous system, but, as age advances, in certain situations, especially within the central parts of the shafts of the long bones, the red marrow tends to undergo a process of physiological "degradation," and the hæmopoietic cells disappear almost entirely from large tracts of the tissue, and the space becomes filled by a development of fat within the connective-tissue cells of the adenoid reticulum (Fig. 369, p. 612). Usually, however, small collections or islets of the blood-forming cells remain towards the periphery of the shaft, and also more especially towards the ends—particularly the proximal ends—of the long bones, a point of great importance, as will be seen later, from the fact that it is from these positions that proliferation may again actively take place should there be any special demand for increased production of blood-cells, either red or white. In the short, flat and irregular bones, especially in the sternum, ribs, vertebræ and cranial bones, the red marrow undergoes this fatty change in lesser degree; though, even in these situations, there is a progressive increase in the amount of fat, which may become considerable in advanced age and in some pathological conditions. There is, therefore, in the red as well as in the fatty marrow, a potentiality for the more active proliferation of the blood-forming elements and for a corresponding diminution or absorption of the fat-cells, should there be a necessity for increased output of the blood-cells formed in the marrow (Plate XVI, and Figs. 363 to 371, pp. 609 to 613).

Yellow or Fatty Marrow. This variety of marrow is found as age advances, more especially in the central parts of the shafts of the long bones, as above described, the fat being developed within the cells of the adenoid reticulum. These areas of fatty marrow form an important potential area for both leucopoiesis and erythropoiesis should there be any special call for the increased proliferation and production of blood-forming cells to combat the attack of disease, or to replace blood-cells which may have been destroyed, for example, in many of the acute and chronic diseases characterised by leucocytosis, or by anæmia. Any factors interfering with or preventing this reaction, *e.g.*, chronic degenerative conditions of the marrow such as may be found in syphilis, chronic alcoholism, lead-poisoning, malignant disease and tuberculosis (especially where there is widespread invasion of the bone-marrow itself by these two diseases), or the too prolonged or repeated action of X-rays, may lead to a rapidly fatal issue if a patient so affected contracts an acute febrile disease such as pneumonia (Plate XVI, Figs. 1 and 2: and Fig. 372). Two of the most important of these degenerative conditions are seen in fibroid or sclerotic, and gelatinous or mucinoid marrows.

Fibroid and Sclerotic Marrow—Myelosclerosis. In old persons, or earlier in life under certain pathological conditions, and more especially in syphilis, the connective-tissue elements may be found proliferating at the expense of the more highly endowed and more delicate and more easily destroyed functioning cells of the tissue. This change may be due to the direct action of some toxic substances, as well as to diminished nutrition from vascular and other derangements. Ossification, partial or complete, may supervene, and the bones may become unduly dense, as in syphilis ; whilst, in other instances, the bony tissue may become partially absorbed and unduly porous (Diseases of Bone, p. 1199, *et passim*).

Gelatinous or Mucinoid Marrow. This is an important degenerative process which may supervene in old age, and especially in chronic debilitating disease accompanied by anæmia, such as cancer, phthisis, etc., in myxœdema, or in starvation and in vitamin-C deficiency (p. 443). It may also occur rapidly in acute diseases such as septic endocarditis, pneumonia, puerperal and other forms of septicæmia, diphtheria, etc., where the organisms or their toxins possess a high degree of virulence (Fig. 362).

Gelatinous degeneration may supervene in both yellow and red marrow, especially when the marrow-tissue has previously undergone prolonged leucoblastic transformation and the proliferative changes have not been kept up, *i.e.*, in exhaustion supervening in an over-active marrow in which the reaction imposes too great a strain on the proliferating cells (Plate XVI, Fig. 6). It is important also to bear in mind that the degeneration can be brought about artificially by the action of certain drugs, which, at first, when given in small therapeutic doses, stimulate the hæmopoietic functions of the marrow, *e.g.*, arsenic, lead, mercury, etc. ; but the prolonged administration or excessive dosage of which may bring about profound gelatinous degeneration, accompanied by disappearance of the blood-forming cells from large tracts of marrow-tissue (p. 12).

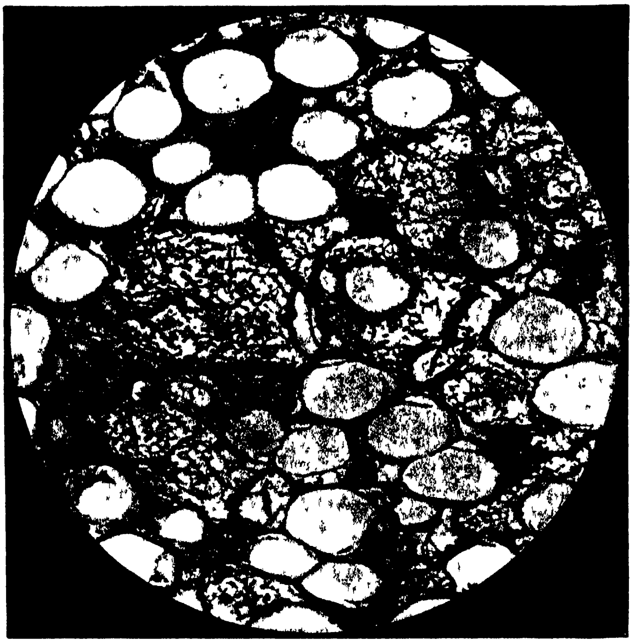


FIG. 362. Gelatinous or mucinoid degeneration of the bone-marrow : transverse section of marrow of femur from a case of septic endocarditis of three weeks' duration, showing high-power view of the more acute form of this degeneration. The fat is undergoing absorption, the cytoplasm of the fat-cells showing mucinoid degeneration. Blood-forming cells are entirely absent. × 200.

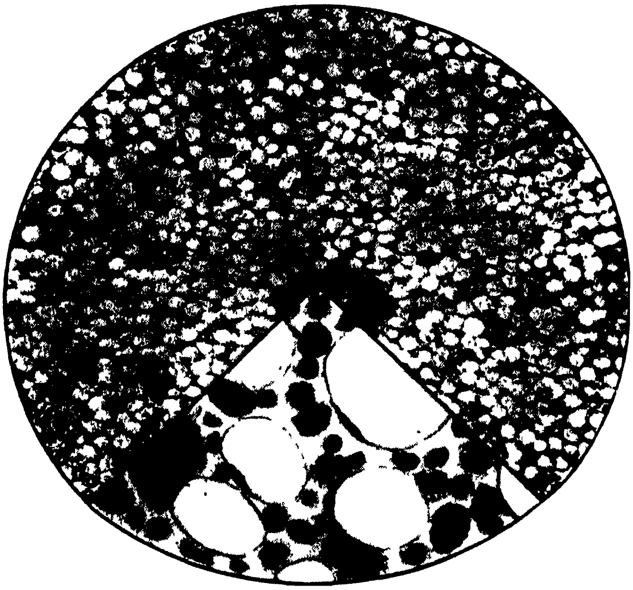


FIG. 363 Transverse section of the bone-marrow from femur of healthy rabbit, showing the average normal proportions of fatty and cellular tissue. Note central venous sinus, a thin-walled vascular space, into which run venous-capillary channels which pass in radially from the periphery towards the centre of the marrow. (*Cf.* Fig. 364, in which these vascular spaces are congested, and therefore show more clearly.) × 45. Inset: The same under a higher power showing cells of the red and the white series and a small megakaryocyte. × 300.

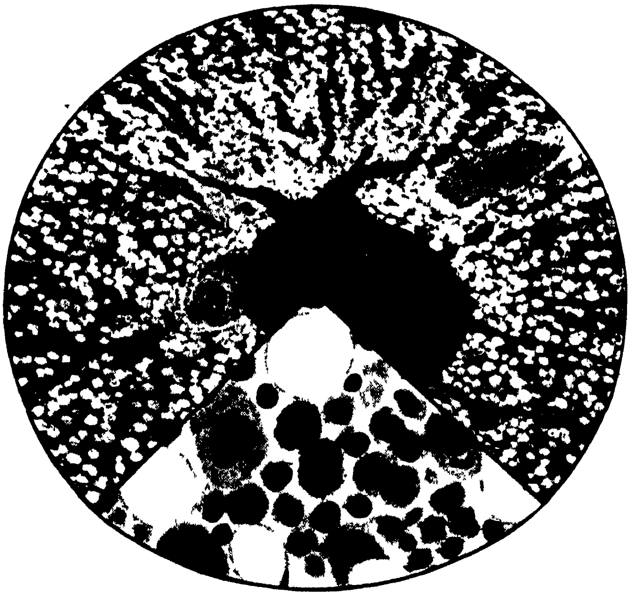


FIG. 364. Transverse section of bone-marrow from femur of rabbit inoculated with pus from pneumococcal empyema (death in eighteen hours), showing congestion of central venous sinus and tributary venous-capillary channels. The medullary artery and some of its branches are also seen in the section. The fat is already slightly diminished, and proliferation of the hæmopoietic cells is just commencing. × 45. Inset: The same under a higher power showing admixture of erythroblastic and leucoblastic cells, etc. × 300.

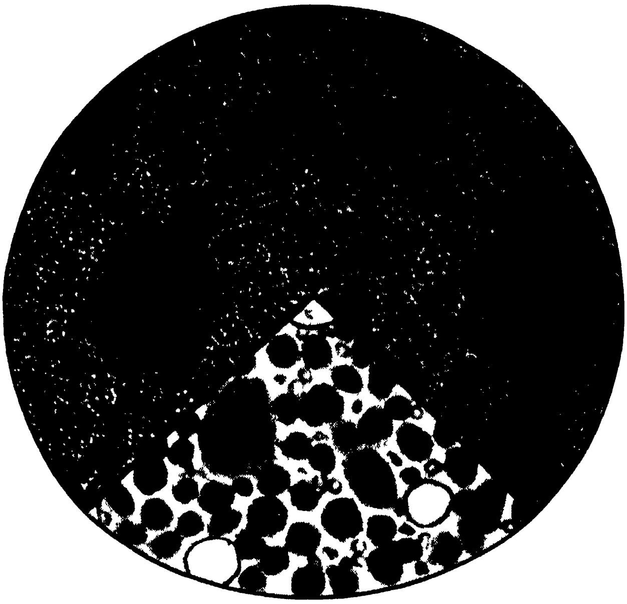


FIG. 365. Transverse section of bone-marrow from femur of rabbit, inoculated with diphtheria-toxin (5 M.L.D.) (death in thirty-three hours), showing intense congestion of the two main tributaries of the central venous sinus and venous-capillary channels. The amount of fat is now greatly diminished, and there is marked proliferation of the blood-forming tissue, corresponding to the leucocytosis observed clinically. × 45.

Inset: The same under a higher power showing details of the hæmopoietic proliferation of both red and white cells, although clinically the blood showed only a polymorphonuclear leucocytosis. A small megakaryocyte is shown. × 300.

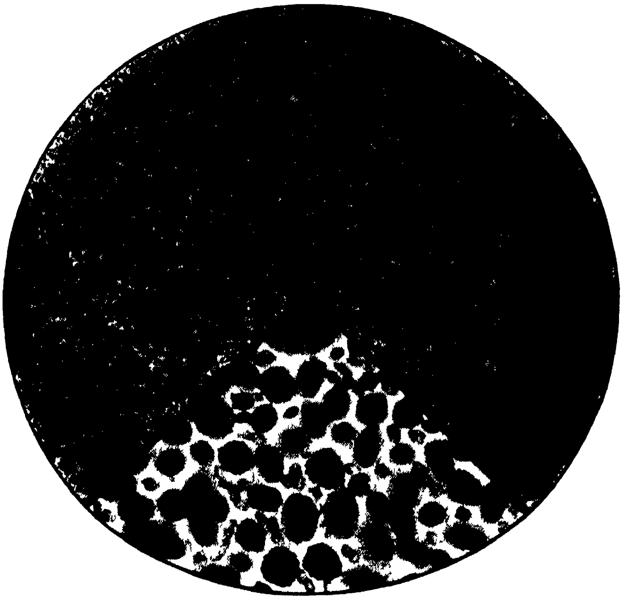


FIG. 366. Transverse section of bone-marrow from femur of rabbit, inoculated with sputum from case of pneumonia containing pneumococci of diminished virulence (death in ten days), showing complete transformation to blood-forming tissue, with total disappearance of the fat-cells. × 45.

Inset: The same under a higher power showing a predominantly leucoblastic reaction. × 300.

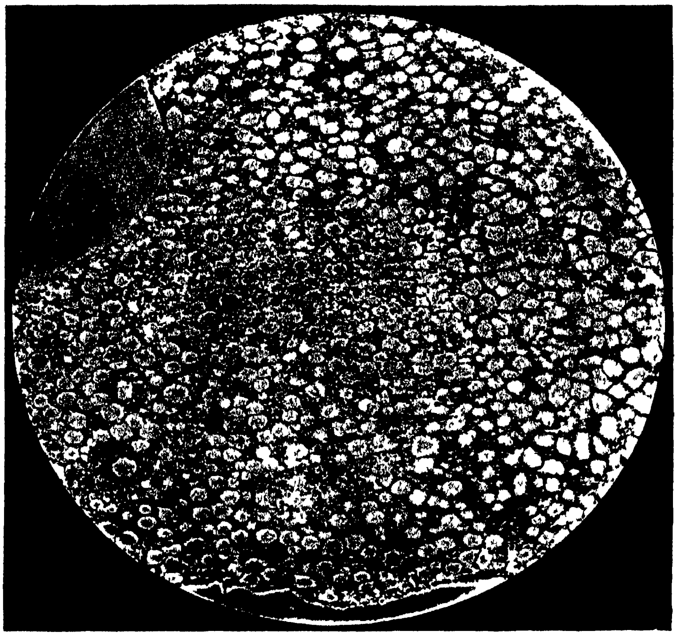


FIG. 367. Section of normal rib marrow from the human subject, showing relative amounts of fatty and blood forming tissue. × 45

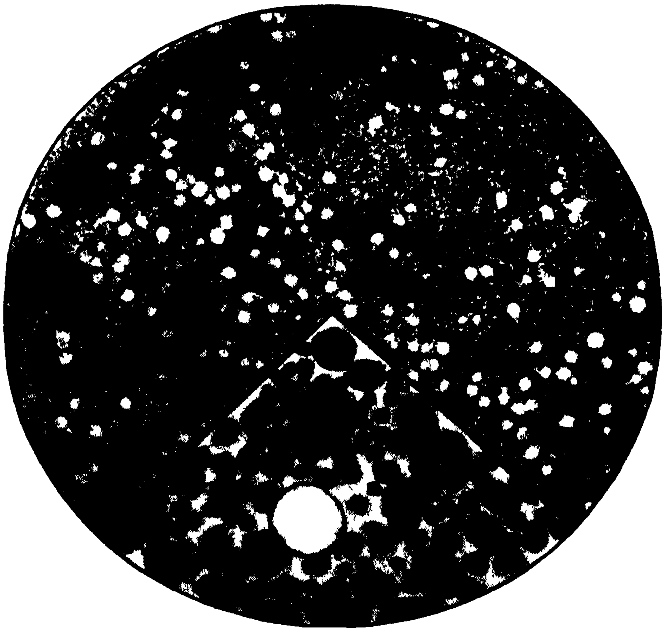


FIG. 368. Section of human rib-marrow from a case of rheumatic pericarditis with leucocytosis, showing comparatively complete leucoblastic transformation, combined, as can be determined when examined under a higher magnification (inset, × 300), with a considerable degree of erythroblastic change, showing as the normoblasts with the small darkly-stained nuclei, i.e., the reaction produced by, and corresponding to, a certain degree of anæmia. Note the few scattered fat-cells of small size still remaining. There has also been some proliferation of the cells of the adenoid reticulum or reticulo-endothelial cells (which take part in the destruction of effete red corpuscles and usually contain varying amounts of residual blood-pigment). × 45.

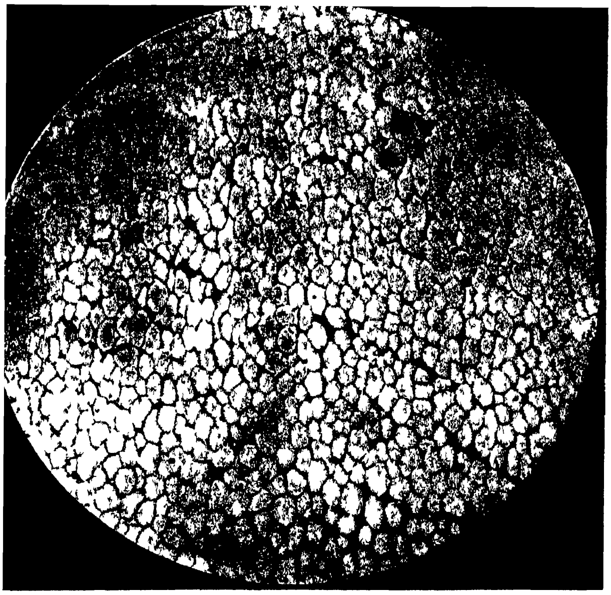


FIG. 369. Transverse section of bone marrow of human femur to show normal appearance of yellow marrow in centre of a long bone. Note the almost complete absence of blood forming cells—only a few small groups being seen. × 45.

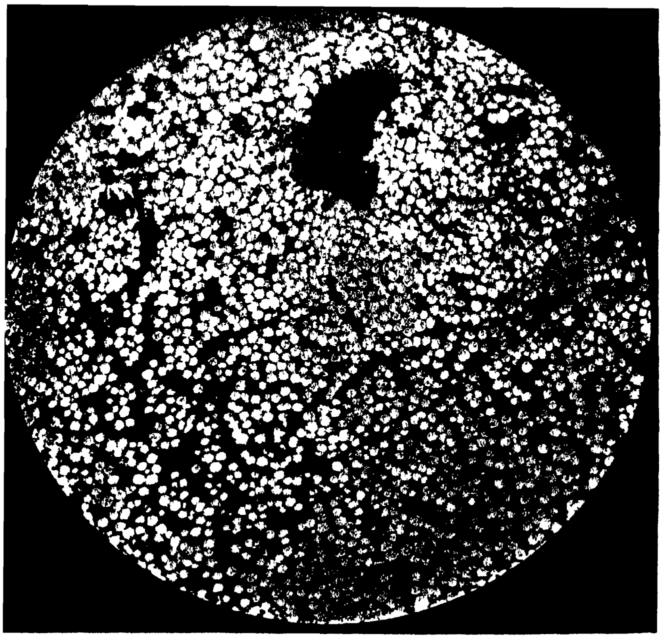


FIG. 370. A similar section of the marrow of the femur from a case of streptococcal septicæmia to illustrate leucoblastic change spreading in from the periphery. The central venous sinus and the accompanying medullary artery are seen towards the upper part of the illustration. × 45.

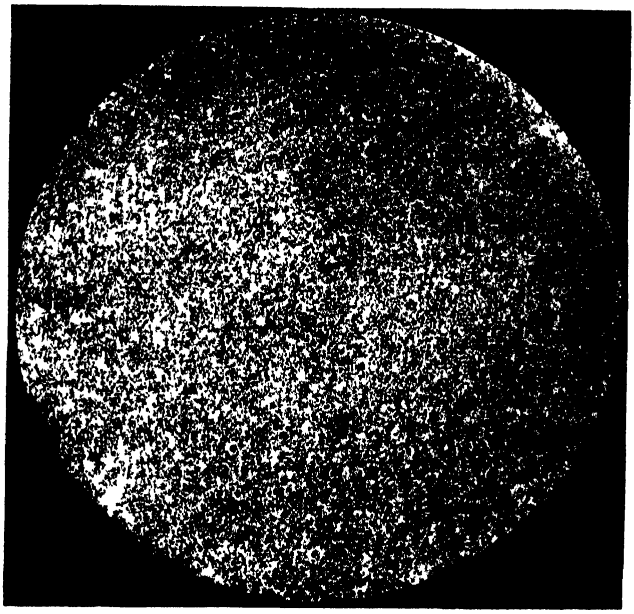


FIG. 371 A similar section of the marrow of the femur from a case of chronic staphylococcal abscesses of six months' duration, the fatty marrow being completely transformed into active blood forming tissue × 45

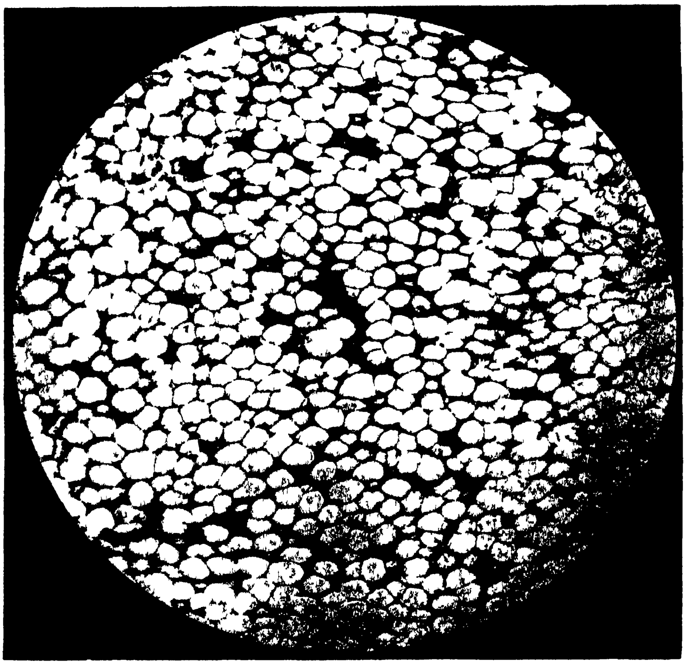


FIG. 372. Transverse section of marrow of femur from a case of pneumonia with leucopenia, to show defective leucoblastic reaction The cellular areas seen are largely engorged capillaries with very little leucoblastic change. × 45.

REACTIONS OF THE BONE-MARROW IN DISEASE

(Plate XVI, and Figs. 363 to 371.)

In many diseased conditions, rapid proliferative changes take place both in the red and in the yellow marrow, and, according as the change is characterised by the increased production of red, or of white, blood-cells, the process is described as being respectively **erythroblastic** or **leucoblastic** in type. In health, there is, in the marrow, a normal balance between these two processes ; and, usually, when, for any reason, the tissue is first stimulated to proliferate, there is increased production of **both** erythrocytes and leucocytes. Soon, however, in most cases, the tissue is found to produce more particularly the variety of cell for which there is special demand, and the reaction becomes either leucoblastic or erythroblastic in type, though both changes may continue to take place simultaneously in the same marrow. A common sequence of events which may be found in certain chronic septicæmias and other diseases is, first of all, with the production of a polymorphonuclear leucocytosis, a slight transitory increase in the number of red corpuscles in the peripheral blood. Then, if the leucocytosis has to be kept up for a prolonged period, the reds become progressively diminished in numbers. If the marrow be examined, corresponding phenomena will be found in it, *i.e.*, the leucoblastic will now predominate over, and obscure, the erythroblastic type of reaction ; and, if the leucocytosis has to be maintained for a still longer period, degenerative changes tend to occur in the leucoblastic marrow, and a progressive anæmia, leading to the appearance of the erythroblastic type of reaction, may supervene. As the anæmia becomes more profound, this too may pass off as exhaustion of the marrow supervenes, and the blood-forming tissue may undergo gelatinous degeneration (p. 608).

Leucoblastic Reaction of the Bone-Marrow :

Neutrophil leucoblastic (or "**myeloblastic**") **reaction** (Plate XVI, Figs. 3, 4 and 5) is the commonest type of change seen, and is found especially in connection with the establishment of an inflammatory leucocytosis, *i.e.*, the increased production of the cells of the neutrophil series, a reaction found in the majority of acute infective diseases, especially when these are due to pyogenic micro-organisms, whether such infections are local (*e.g.*, inflammation, abscess-formation, etc., due to the presence of staphylococci and streptococci, *Bact. coli*, and many other micro-organisms), or general as in pneumonia or the septicæmias. The results produced in the marrow are practically identical in both sets of cases, and any variations in degree are due rather to the intensity, quality, and amount of the irritant, than to its special point of attack and distribution in the body. This leucoblastic reaction is, naturally, most readily produced in the red marrow (Figs. 367 and 368), where the increased proliferation of the special variety of hæmopoietic cell required—in this case the neutrophil myelocytes—will occur. If further demands are made upon the reacting bone-marrow, the proliferative change spreads into the fatty or yellow marrow in the shafts of the long bones and elsewhere (Figs. 369 and 370) ; and, in these situations, all degrees of the reaction may be observed, up to complete transformation into fully formed red marrow. In the case of the long bones, this transformation spreads into the fatty marrow from the periphery and ends of the shaft, *i.e.*, from the situations in which the hæmopoietic cells have not completely disappeared during the physiological degradation of the marrow to fatty tissue. Any pathological states preventing this leucoblastic reaction, *e.g.*, the presence of fibroid or gelatinous degeneration (Fig. 362), may determine a rapidly fatal issue in a given case, say, of pneumonia or diphtheria; and these may thus be characterised clinically by the absence of leucocytosis or by leucopenia, *i.e.*, a diminution in the number of the leucocytes (pp. 621 and 637).

Occasionally, the leucoblastic reaction is of a different type, as in those cases in which the peripheral blood contains undue numbers of leucocytes of other than neutrophil type. Of these may be mentioned an **eosinophil leucoblastic reaction,** in which there is increase of the eosinophil granular cells. As stated on p. 623, however, the numbers of these in the marrow and in the circulating blood appear often to show no very definite relationship to each other. Mention may also be made here of the bone-marrow " reaction " in the **leukæmias,** the possible nature of which group of marrow- and blood-disorders is discussed on p. 625 *et seq.* In myeloid leukæmia, there is profound and intense leucoblastic proliferation, and in the chronic form of the disease, even the long bones contain an abundance of greyish-pink marrow. Primitive cells—the precursors of the granular series of blood-cells—are present in great abundance, including many myeloblasts. In lymphatic leukæmia, the proliferated bone-marrow is often rather more reddish in colour, owing to the greater degree of erythroblastic reaction which tends to accompany the leucoblastic changes. Megakaryocytes are usually diminished in the lymphatic form, whereas in the myeloid variety they tend to be increased in numbers, especially in the earlier stages. Whether these leukæmic changes are of the nature of a reaction of the marrow to some unknown " irritant " ; are due to lack of the requisite maturation-factors; or are neoplastic in nature is still unknown; but, " under experimental cultural conditions, the leukæmic marrow-cells develop in a manner resembling normal," the primitive cells growing into more mature types of their own granulocyte- or monocyte-series in about two weeks (Israëls [1]) —a finding which appears to be in favour of the second of these hypotheses.

Erythroblastic Reaction of the Bone-Marrow :

Two main types of this occur :—

Normoblastic—*i.e.*, bone-marrow in which normoblasts or normal nucleated red cells are found in excess, *e.g.*, after hæmorrhage, and in most " secondary " anæmias, where the tissue endeavours to compensate for the deficiency in the number of the red corpuscles of the blood. This change, as already explained, may also supervene in leucoblastic marrows which are becoming exhausted.

Macroblastic and megaloblastic—where there is reversion to a more primitive type of erythropoiesis. **Megaloblasts**—or nucleated red cells of abnormally large size,[2] and possessing nuclei of primitive type—are increased in number in the marrow in certain diseases, both acute and chronic. They are usually only scanty in number, although in some cases of exophthalmic goitre, malignant disease, tuberculosis, many acute and septic conditions, typhoid fever, etc., they have been observed with comparative frequency, and sometimes even in considerable numbers.[1] It is a matter of great importance whether their cytoplasm is or is not **hæmoglobinised** (p. 595); and, except in the fœtus, the **fully hæmoglobinised megaloblast** is pathological, and is found in greatest numbers (both in blood and bone-marrow) in untreated cases of Addisonian anæmia (Plate XVIII, Fig. 4, facing p. 650), and also in some cases of myeloid leukæmia. As will be understood from a reference to Fig. 360, p. 593, a certain degree of **macroblastic** proliferation is almost always found as an accompaniment of increased normoblastic erythropoiesis.

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[1] "The Nature of Human Leukæmia: Evidence from the Culture of Bone-Marrow Cells *in Vitro*," *Jour. Path. and Bact.*, 1940, **51,** 235.

[2] NOTE. For the classification of these cells, the primitive characters of the nucleus, as well as the presence or absence of hæmoglobin in the cytoplasm, are of much greater significance than the mere size of the cell.

In the condition known as "aplastic anæmia," which might with greater accuracy be termed a "hypoplasia" (since complete "aplasia" would, of course, be incompatible with life) the erythroblastic power of the marrow becomes progressively diminished. Prolonged exposure to the more penetrating varieties of X-rays may bring about this grave condition, hence the necessity for care in the extensive, prolonged, or repeated administration of these to patients, as well as of precautions for the protection of radiologists and their assistants.

FUNCTIONS OF THE BONE-MARROW

These may be briefly recapitulated as follows :—

(1) **Hæmopoietic Functions.**

(*a*) **Erythroblastic.** The formation of red corpuscles.

(*b*) **Leucoblastic.**[2] The formation of white blood-cells, especially those of the granular series.

A normal balance between these two processes is maintained in health (p. 604 and Table on p. 605); whilst, in disease, there is a latent capacity for the increased production of any or all of the blood-cells to meet the increased demand for them, whether this be due to the necessity of replacing those destroyed by the disease, as in the anæmias, or to the fact that more blood-cells are required to combat the attack of the invading bacterial or other pathogenic agent, as is seen in the various inflammatory and suppurative conditions—the fatty marrow forming an important potential additional area for the production of this reaction in the marrow (p. 607).

(*c*) **Platelet-Formation.** The part played by the megakaryocytes of the marrow in the production of these is discussed on p. 601.

(2) **Blood-Destruction, Phagocytosis, etc.**

Balanced blood-formation and blood-destruction are constantly going on in health, and the marrow not only produces red and white blood-cells but, like the liver and spleen, has a rich and abundant reticulo-endothelial system, the phagocytic activity of which is increased in most of the acute and chronic toxic diseases, *e.g.*, the acute infective fevers, septicæmias, malaria, etc.: the

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[1] Carnegie Dickson, *loc. cit.*, p. 62. (*See* our footnote on p. 603.)

[2] The word "**myeloblastic,**" as a contraction for "**myelocytoblastic,**" is used by some writers as synonymous with "**leucoblastic.**"

DESCRIPTION OF PLATE XVII

PLATE XVII [1]

Various forms of phagocytic cells, pigment-cells, etc., found in the bone-marrow

NOTE. In order to differentiate the nuclei of the phagocytic cells themselves f those belonging to cell-inclusions within their cytoplasm, the letter " a " has b inserted in the former where necessary.

FIG. 1. From a case of acute streptococcal septicæmia in a girl aged 16, showing endothelial cells of a capillary and of the reticulo-endothelial tissue becon amœboid and phagocytic.

FIG. 2. From a case of severe anæmia in a woman of 48 in which there were l numbers of these endothelial cells actively phagocytic to the red corpuscles filled with golden-brown blood-pigment.

FIG. 3. From a case of tuberculous peritonitis of eleven days' history in which eos phils were very numerous in the marrow and were being englobed in consider numbers by large phagocytic cells of reticulo-endothelial type.

FIG. 4. From a case of streptococcal puerperal septicæmia of seven weeks' duratic a woman of 35, in which the actively phagocytic reticulo-endothelial cells developed into large, actively hæmolytic, multi-nucleated plasmodial ma demonstrable in fresh wet films, but practically invisible in ordinary sections.

FIG. 5. From the same case as Fig. 2, but from a paraffin-section preparation, phagocytic cells containing numerous cell-inclusions, especially red corpuscles their residual blood-pigment. In some of the phagocytic cells (*e.g.*, that in u right corner) only nucleated red corpuscles had been englobed, in others m mature erythrocytes and the pigment derived from them.

Fig. 6. From a case of (untreated) " pernicious anæmia " in a female aged 39, four years' history. This film-preparation demonstrated very numerous actively hæmolytic phagocytic cells, containing mostly red corpuscles, occasionally nucleated. In some of these phagocytes the englobed erythroc numbered several dozen, and, where these had undergone digestion, much resi pigment remained.

FIG. 7. From a case of pneumonia with leucopenia: section showing num phagocytic reticulo-endothelial cells containing golden-brown blood-pigmen a small island of mixed blood-forming tissue.

FIG. 8. From a case of pneumonia with leucopenia in a male aged 44, ill for ten A single large plasmodial endothelial cell in a fresh-wet film from the rib-ma crowded with erythrocytes, erythroblasts, blood-pigment and myelocytes. two nuclei of the cell itself are indicated by the letter " a " on them.

FIG. 9. From a case of acute streptococcal septicæmia in a male aged 46: par section showing cells crowded with blood-pigment.

FIG. 10. From a case of sarcoma of the kidney in a man of 61 years, with a cli history of eight months. A section showing a similar increase in the numb phagocytic cells containing much residual blood-pigment. An excess of eosin myelocytes, numerous normoblasts, and a few myelocytes are shown.

Figs. 1, 5, 7, 9 and 10 are from paraffin-sections.
Figs. 2, 3, 4, 6 and 8 are from wet-fixed films.
All these preparations were stained with methylene blue and eosin. × 600

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[1] Reduced from the original coloured Plate VII, Carnegie Dickson's " The Bone- Longmans, Green and Co., London, 1908.

PLATE XVII, p. 616

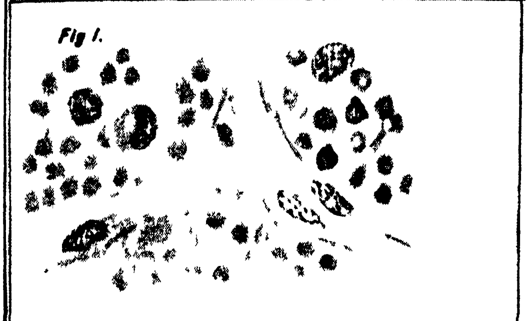
Fig 1.

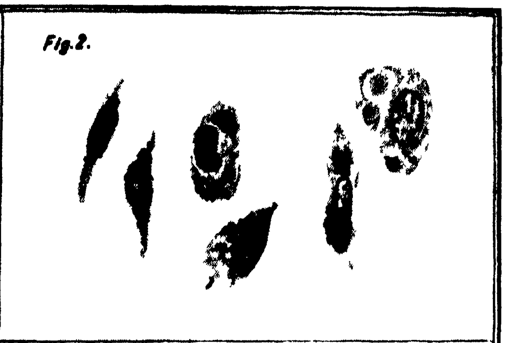
Fig. 2.

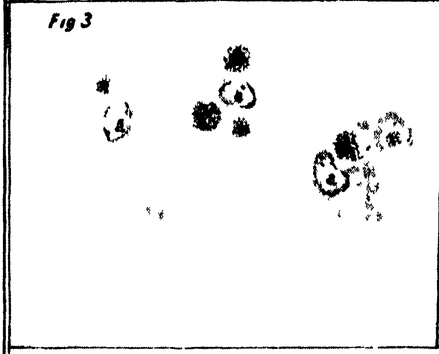
Fig 3

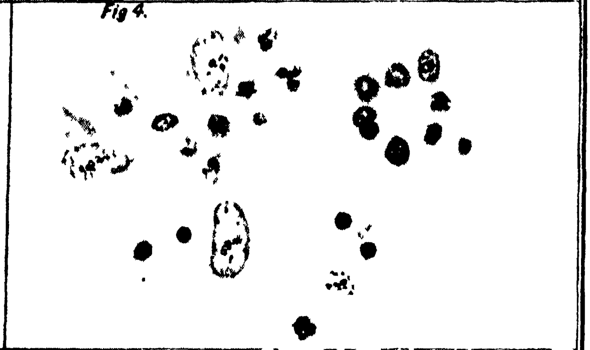
Fig 4.

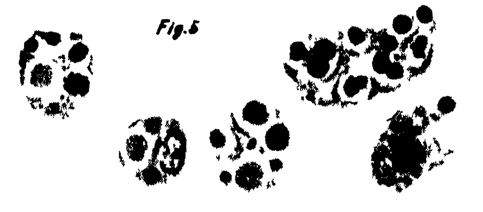
Fig. 5

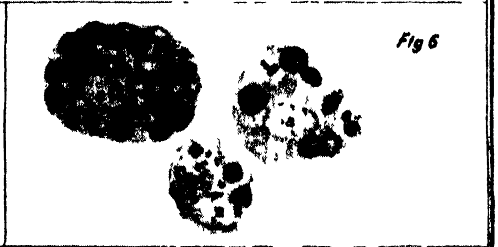
Fig 6

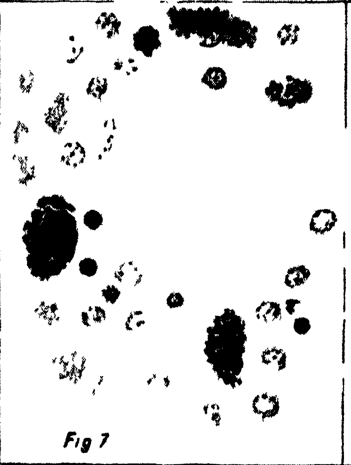
Fig 7

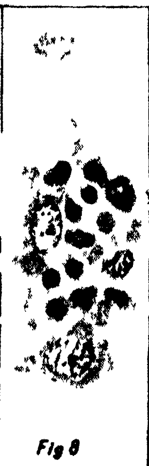
Fig 8

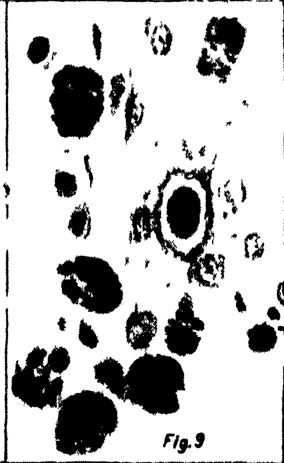
Fig. 9

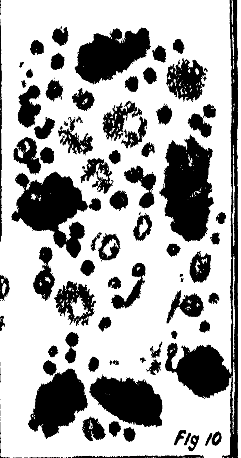
Fig 10

PLATE XVII[1]

Various forms of phagocytic cells, pigment-cells, etc., found in the bone-marrow.

NOTE. In order to differentiate the nuclei of the phagocytic cells themselves from those belonging to cell-inclusions within their cytoplasm, the letter "a" has been inserted in the former where necessary.

FIG. 1. From a case of acute streptococcal septicæmia in a girl aged 16, showing the endothelial cells of a capillary and of the reticulo-endothelial tissue becoming amœboid and phagocytic.

FIG. 2. From a case of severe anæmia in a woman of 48 in which there were large numbers of these endothelial cells actively phagocytic to the red corpuscles and filled with golden-brown blood-pigment.

FIG. 3. From a case of tuberculous peritonitis of eleven days' history in which eosinophils were very numerous in the marrow and were being englobed in considerable numbers by large phagocytic cells of reticulo-endothelial type.

FIG. 4. From a case of streptococcal puerperal septicæmia of seven weeks' duration in a woman of 35, in which the actively phagocytic reticulo-endothelial cells had developed into large, actively hæmolytic, multi-nucleated plasmodial masses, demonstrable in fresh wet films, but practically invisible in ordinary sections.

FIG. 5. From the same case as Fig. 2, but from a paraffin-section preparation, showing phagocytic cells containing numerous cell-inclusions, especially red corpuscles and their residual blood-pigment. In some of the phagocytic cells (*e.g.*, that in upper right corner) only nucleated red corpuscles had been englobed, in others mainly mature erythrocytes and the pigment derived from them.

Fig. 6. From a case of (untreated) "pernicious anæmia" in a female aged 39, with four years' history. This film-preparation demonstrated very numerous large actively hæmolytic phagocytic cells, containing mostly red corpuscles, only occasionally nucleated. In some of these phagocytes the englobed erythrocytes numbered several dozen, and, where these had undergone digestion, much residual pigment remained.

FIG. 7. From a case of pneumonia with leucopenia: section showing numerous phagocytic reticulo-endothelial cells containing golden-brown blood-pigment, in a small island of mixed blood-forming tissue.

FIG. 8. From a case of pneumonia with leucopenia in a male aged 44, ill for ten days. A single large plasmodial endothelial cell in a fresh-wet film from the rib-marrow, crowded with erythrocytes, erythroblasts, blood-pigment and myelocytes. The two nuclei of the cell itself are indicated by the letter "a" on them.

FIG. 9. From a case of acute streptococcal septicæmia in a male aged 46: paraffin-section showing cells crowded with blood-pigment.

FIG. 10. From a case of sarcoma of the kidney in a man of 61 years, with a clinical history of eight months. A section showing a similar increase in the number of phagocytic cells containing much residual blood-pigment. An excess of eosinophil myelocytes, numerous normoblasts, and a few myelocytes are shown.

Figs. 1, 5, 7, 9 and 10 are from paraffin-sections.
Figs. 2, 3, 4, 6 and 8 are from wet-fixed films.
All these preparations were stained with methylene blue and eosin. × 600 (approx.

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[1] Reduced from the original coloured Plate VII, Carnegie Dickson's "The Bone-Marrow, Longmans, Green and Co., London, 1908.

PLATE XVII, p 616

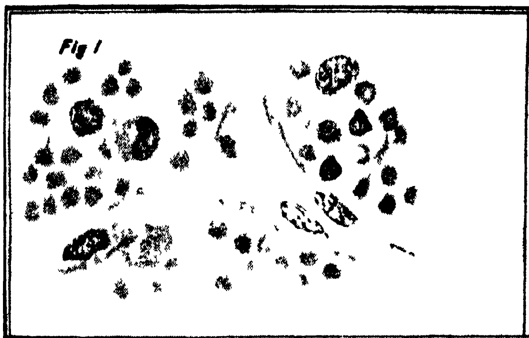
Fig 1

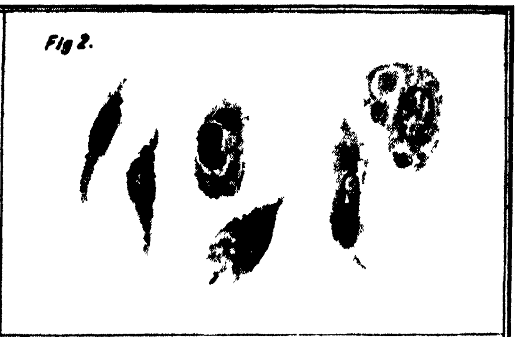
Fig 2.

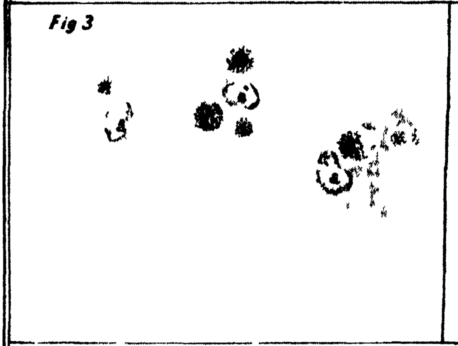
Fig 3

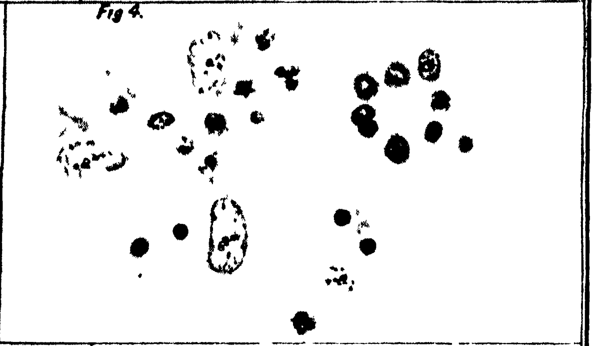
Fig 4.

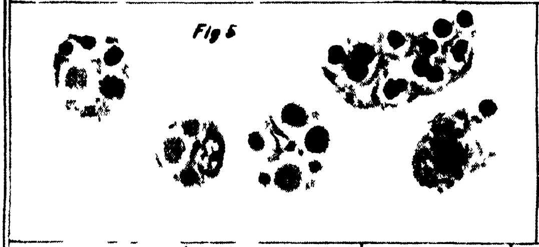
Fig 5

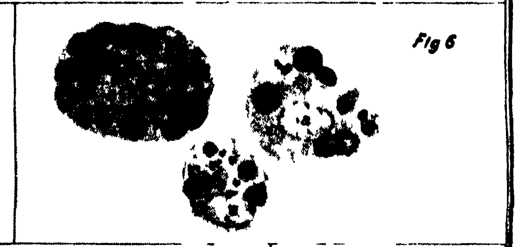
Fig 6

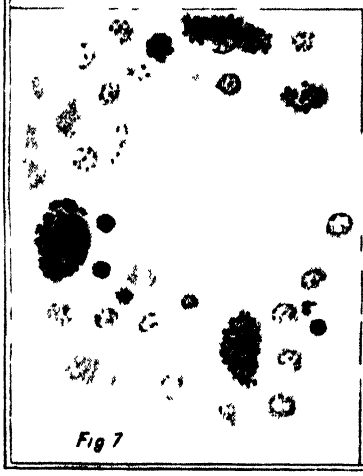
Fig 7

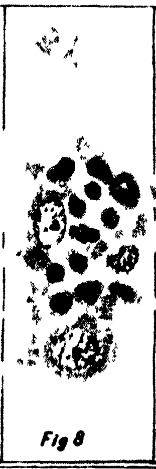
Fig 8

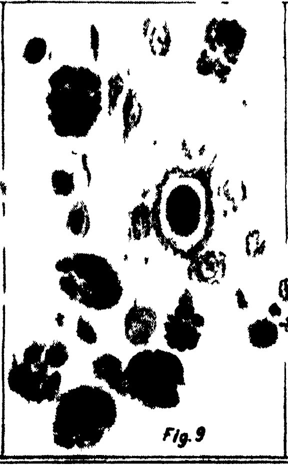
Fig. 9

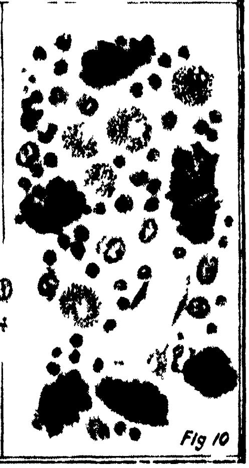
Fig 10

anæmias and the "cachexias," especially malignant disease; and, in consequence, blood-destruction and phagocytosis of especially the red corpuscles are pronounced features in such pathological conditions (Plates XI, opposite p. 222, Fig. 2 : XIII, opposite p. 380, Fig. 4 : and XVII, opposite p. 616).

Phagocytosis of pathogenic organisms also occurs to a considerable degree in many diseases, the marrow being specially liable to invasion by micro-organisms ; and, as in the case of the spleen, pure cultures can frequently be obtained from this tissue by sternal puncture (" medulloculture "), *e.g.*, in typhoid fever, the pneumonias, and in streptococcal and other septicæmias (p. 606). Some blood- and other parasites pass certain stages of their development in the bone-marrow, and endothelial and other forms of phagocytic cells may contain englobed parasites or their remains, *e.g.*, in malaria, trypanosomiasis and kala-azar (p. 606).

(3) **Functions in Relation to General Nutrition and especially with regard to Metabolism of Fat.** Fatty or yellow marrow is richly supplied with blood-vessels ; and, in fevers, etc., the fat may be rapidly absorbed from the tissue, which acts as a storehouse for this substance (p. 194). It has been suggested that the red marrow, like many of the glandular organs in the body, may give rise to internal secretions of importance in general nutrition and metabolism ; but, owing to the impossibility of experimentally eliminating the action of the tissue on account of its wide anatomical distribution, it is difficult to prove the truth of this supposition.

LEUCOCYTOSIS

A definite increase in the number of leucocytes above normal is—except in the case of certain so-called " blood-diseases " such as the leukæmias—termed a **leucocytosis.** In healthy young adults and middle-aged persons, the average normal number of leucocytes in the peripheral capillary circulation, as judged from the blood obtained under properly regulated conditions by pricking the ear-lobe or finger, is **8,000 per c.mm.,** with a variation of perhaps 500, or at all events not more than 1,000 above or below that figure. Much greater variations, *e.g.*, from 5,000, or even as low as 4,000, up to 10,000, are sometimes stated to be the lower and upper " normal " limits respectively ; but it must be emphasised that such figures are often founded upon the findings in a hospital- or semi-invalid population : or at all events not in robust and healthy persons : and with no attempt to systematise the time of day and conditions of examination. It should be our practice to make all blood-counts under as uniform conditions as possible, for this is quite as important as it is in the making of a blood-sugar or a blood-urea estimation. A useful routine method to adopt is to take the specimens, preferably about the same time of day, some three hours after a meal, say at 11 a.m. or 12 noon, after a light breakfast at 8 or at 9 a.m. Moreover, variations in number of the corpuscles, both red and white, especially in the direction of diminution, in persons regarded as " healthy " are often due to the action of some slight but long-continued and perhaps unsuspected infection say of a para-nasal sinus or a dental root. Indeed, for the diagnosis of the presence of such conditions of chronic focal sepsis, the finding of a mild degree of leucopenia is often a valuable aid. Similarly, a red count of, say, 4,500,000 or 4,750,000 and a hæmoglobin-estimation of 85 to 90 per cent., obtained, for example, in town-dwellers in what is sometimes regarded as "ordinary average health," are really much below what we consider the normal standard for such individuals. We have had the opportunity, over many years, of examining the blood of healthy young adults, especially in the army, and our "normal standard" is certainly higher than the figures given in some textbooks. Similarly, 3, 4, and even 5 per cent. of eosinophils are sometimes stated to be "normal," but are in reality to be regarded more frequently as evidence of the presence of some foreign-protein susceptibility (p. 599).

An **increase** in the total leucocyte-count up to 12,000 or 15,000 per c.mm. does certainly occur in some physiological conditions, such as after exercise or after bathing (see below under "Clinical Varieties of Leucocytosis"), but routine blood-counts to be of diagnostic value are not usually made after such preliminaries. In many pathological conditions, counts of 20,000 to 30,000 per c.mm. may frequently be obtained ; and in exceptional circumstances the count may rise even to 60,000 or 70,000, or more. **Diminution** in the number of white cells—more particularly the polymorphs—may be seen as a transitory phenomenon preceding the establishment of a leucocytosis in some cases of acute disease. This may be due to two different sets of causes : (1) partial withdrawal of the cells from the peripheral circulation with accumulation in the internal organs and hence a lowered number in the blood examined, or (2) defective formation, and hence defective replacement of any withdrawn from the circulation. In the latter event the deficient reaction may persist, if the infection is especially virulent or if the patient is enfeebled and his blood-forming tissues exhausted by old age, chronic alcoholism or syphilis. Acute miliary and other uncomplicated forms of tuberculosis, typhoid fever, influenza and measles are *not* characterised by the presence of a leucocytosis, and diminution in the number of white cells occurs in some cases of starvation and malnutrition as well as in Addisonian, splenic, and certain "secondary" anæmias.

Varieties of Leucocytosis. These may be divided into those which are respectively physiological, experimental and therapeutic, and pathological. In the first of these categories come the leucocytosis of digestion, which does not usually exceed 15,000 white cells per c.mm., the lymphocytes especially being increased : the leucocytosis of the new-born infant, which may be from 14,000 to 20,000, or more : the leucocytosis of pregnancy (12,000 to 18,000), and that following parturition (up to 25,000) : and the leucocytoses following violent exercise, the use of cold baths, etc. The considerable leucocytosis, chiefly polymorphonuclear, which follows an epileptic seizure, may perhaps be akin to that seen after violent exercise. The "leucocytosis induced by violent emotion" may be due to stimulation of the ductless glands, *e.g.*, the suprarenal (*see* below). In some of these conditions, the increase in the number of the leucocytes in the peripheral circulation is due to redistribution from internal organs rather than to any increased production of them by the bone-marrow and other blood-forming tissues.

Certain experimental and therapeutic measures may lead to the production of leucocytosis: for example, the giving of drugs and chemicals such as the salicylates, quinine, potassium chlorate, phenacetin, or the inhalation of chloroform. Leucocytosis may also occur in poisoning with coal-gas and chronic lead-poisoning. Similarly, a considerable increase can be induced by the administration of certain animal extracts, for example of the thyroid, suprarenal, or bone-marrow, and of nuclein and nucleic-acid derivatives, substances which have been employed for the artificial stimulation of leucocytosis. In surgical practice, a post-operative rise is frequently observed, even in aseptic cases. The leucocytosis produced by therapeutic inoculation with certain bacterial vaccines and toxins is identical in its nature with the same condition produced by disease, and, therefore, calls for no further comment here. In streptococcal and other infections characterised by leucopenia in place of the usual leucocytosis, a therapeutic leucocytosis may be stimulated artificially by the intravenous injection of horse-serum; and in other more chronic cases of leucopenia a similar result may be obtained by the intramuscular injection of pentide or pentnucleotide (pentose nucleotide), a drug used for the treatment of agranulocytosis (p. 637).

Leucocytosis produced by Disease. The most important variety of leucocytosis so produced is that seen in the majority of **inflammatory** and in many **toxic** diseases. An increase of the white cells—more especially of the polymorphonuclear cells—occurs in most of the acute infective diseases, notably in pneumonia, acute rheumatism, and diphtheria. Exceptions to this general rule are found in typhoid fever, influenza, measles, and also in tuberculosis; and, if a polymorphonuclear leucocytosis is discovered in patients suffering from these diseases, the presence of some complication, such as pneumonia, suppuration, or other inflammatory condition, is to be suspected.

Inflammatory and toxic leucocytosis is found, not only when the disease is **general,** but also when the lesion is **localised,** for example, in local inflammatory and suppurative conditions such as abscess or appendicitis, and its occurrence is of great value in the diagnosis of these conditions.

A rise in the leucocyte-count may occur in certain parasitic diseases. In these, the increase may affect especially certain varieties of white cell other than the neutrophil leucocytes. Thus, in many skin-diseases and parasitic intestinal infestations, there may be an eosinophilia; and in malaria, the large hyaline mononuclear cells or monocytes are increased.

Cardiac disease may produce leucocytic changes as part of the circulatory disturbance which often results and which is due mainly to capillary stasis. In paroxysmal tachycardia, however, there is a leucocytosis up to 20,000 to 30,000 cells per c.mm. with each paroxysm; whilst in coronary thrombosis a relatively persistent leucocytosis is commonly found.

Post-hæmorrhagic leucocytosis is a well-recognised phenomenon. Loss of blood stimulates the general hæmopoietic activities of the bone-marrow, and leads, at first, to increased production both of red and of white cells, *i.e.*, both of the main types of blood-cells produced by the tissue, as well as of blood-platelets. Later, the marrow adjusts its output to the particular circumstances of the case; and the special type of change required—in this instance mainly erythroblastic—is established, in order to replace the red corpuscles lost by the hæmorrhage (*cf.* p. 663).

Terminal or Ante-mortem Leucocytosis. Sometimes a considerable increase of white cells in the peripheral circulation occurs in patients who are moribund. In some instances, this may be due to the presence of terminal bacterial infection ; but a remarkable tendency of the polymorphonuclear cells to leave the marrow at or just before death has been observed by several writers, and no doubt accounts for the increase, in many cases, of these cells in the blood at this period.

Cytological Types of Leucocytosis

1. **Neutrophil or Polymorphonuclear Leucocytosis** (Plate XV, facing p. 596, Fig. 2). In the majority of inflammatory and allied diseases, it is especially the cells of the finely granular neutrophil series or granulocytes that are increased. The cells of this series found in the blood in such cases may not be, and, in fact, most commonly are not, entirely confined to the mature or fully developed polymorphonuclear members of the neutrophil group—though, as a rule, these cells greatly predominate. The immature intermediate cells of the series, and even the parent-myelocytes themselves, may occur in considerable numbers ; and the condition is, therefore, most accurately described as a **neutrophil leucocytosis**. The number of these cells, and also their degree of development or maturity, depend upon various factors, more especially upon the nature, quality, intensity, and duration of application of the causal irritant, and also upon the age and vitality of the patient, and the healthy condition or otherwise of the hæmopoietic tissue of the bone-marrow. It is largely upon these phenomena that the **Arneth-** (simplified by Cooke and Ponder) and the **Schilling-counts** are based, particular attention having been directed to the enumeration of the number of lobes in, and other characters of, the nuclei of the polymorphs and any of their predecessors which find their way into the peripheral circulation. These lobes are fewer in number in the more immature cells of the series, and *vice versâ* (*see also* p. 598). For details of these procedures, books on clinical methods and on clinical hæmatology may be consulted.

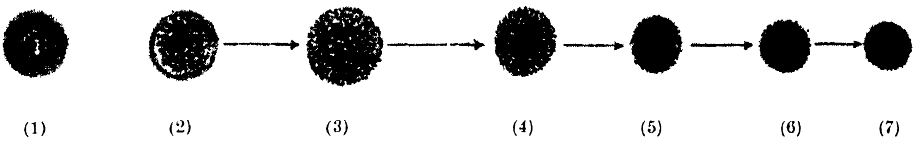

Fig. 373. Diagram showing the cytogenesis of the neutrophil-leucocyte series in the bone-marrow, from (1) the non-granular myeloblast, developing (2) cytoplasmic granules and becoming a promyelocyte, which by mitotic division forms (3) larger and (4) smaller myelocytes, which then pass through the stages of (5) metamyelocyte or proleucocyte and (6) immature and finally (7) the mature or "adult" polymorphonuclear leucocyte of the blood.

Peroxidase Staining-Reaction. By the specific colour-reaction of the **oxidase-granules** in their cytoplasm obtained by this method, the cells of the **granulocyte-series** (neutrophils and eosinophils, and perhaps also the basiphils) can be differentiated from the cells which do not possess these granules, viz., lymphocytes and lymphoblasts and most of the cells of the monocyte and monoblast.series (unless, as sometimes happens, the monocytes have taken up granulocytes or their remains by phagocytic action). The reaction can therefore be employed to differentiate the types of leukæmia from one another (pp. 628 and 631–2).

Certain irritants appear to have the capacity of attracting leucocytes towards them, this phenomenon being termed **positive chemotaxis** (or **chemiotaxis**); whilst others do not possess this power (in this connection see also under "Causes of Leucocyte-Emigration" in Chapter II on "Inflammation," pp. 34–5). In positive chemotaxis, the leucocytes are attracted towards the seat of irritation and may pass from the vessels in large numbers. In order to meet the increased demand for such cells, greater numbers pass from the marrow into the blood; and, if the demand be sufficient in intensity and duration, the blood-forming tissue of the marrow proliferates to supply it, as has already been described on p. 614. It has also been noted that the occurrence of this leucoblastic reaction of the bone-marrow may be prevented by previous degeneration or exhaustion of the tissue by such conditions as syphilis, alcoholism, etc. In these cases—the capacity for responding to the increased call being diminished or lost—the supply of leucocytes may be even less than normal. Absence of any increase is termed **aleucocytosis**; whilst a diminution in the normal leucocyte-count is known as **leucopenia**—these conditions being not infrequently seen in pneumonia occurring in alcoholic subjects—pneumonia with leucopenia, a serious disease which may lead to a rapidly fatal issue in profound infections, and in its most extreme form in **agranulocytosis** (pp. 16 and 636–7), in which there is interference with the normal process of maturation of the granulocytes in the bone-marrow.

Where the demand for an increased supply of leucocytes is moderate and the patient has been previously in good health, the leucocyte-count may number, say, 10,000, 12,000, or 14,000. A more serious call may lead to an increase to 18,000 or 20,000; whilst in severe cases, say of appendicitis or of pneumonia, the count may be 25,000, 30,000, or 40,000. When the power of resistance has been lowered by previous disease or other cause, the leucocytes, as noted on p. 618, may reach the number of 60,000 or 70,000, or even more. Thus, in the most serious cases—those of severe disease in debilitated subjects—the reaction may either be deficient or absent, or it may be excessive in degree.

In the milder forms of leucocytosis, the increase is almost entirely one involving the mature or fully-developed polymorphonuclear neutrophil cells, though a certain number of slightly immature forms are found (Fig. 373). When the call is more severe, many immature polymorphs, and perhaps some intermediate myelocytes (by some called "metamyelocytes" or "proleucocytes") with horseshoe-shaped nuclei, appear in the blood; whilst in severe cases, *e.g.*, of pneumonia, about the period of crisis, it is by no means uncommon to find a number of neutrophil myelocytes—sometimes as many as 10 per cent. or more —in the blood. Large numbers of *myelocytes are found in the blood of smallpox* cases; and, in serious or fatal cases of diphtheria in children, the occurrence *of as many as 16 per cent. has been recorded.*

*2. **Lymphocytosis** is more frequently a relative than an absolute increase of lymphocytes, the latter being seen comparatively rarely except in certain infections in infants, and especially in congenital syphilis: and in children and* adolescents in whooping-cough, measles, chickenpox and mumps: whilst in them and in older persons any lymphocytosis present in influenza, undulant fever, and in tuberculosis, is often rather a relative than an absolute increase of these cells. In typhoid fever, there is usually a neutrophil leucopenia, producing a relative lymphocytosis or there may be also an increase in the absolute numbers of the lymphocytes and perhaps of the large monocytes.

Glandular fever (infectious mononucleosis) is also associated with an absolute lymphocytosis—perhaps 50 to 75 per cent. of a total count of up to 20,000 or 30,000 white cells—which is noticeable especially in the convalescent stages of the disease (p. 683).

Increase of lymphocytes or lymphocyte-like cells in leukæmia and in some sarcomatous tumours of lymphatic glands, and the differential diagnosis of these from glandular fever, are dealt with in the sections on these diseases (pp. 631–636 and 683).

3. **Monocytosis, or Increase of the Monocytes or Large Hyaline Mononuclear Cells.** An absolute increase of these cells occurs in monocytic leukæmia, in glandular fever and in some cases of subacute bacterial endocarditis. Relative increase in numbers also takes place in some diseases, notably in malaria, in which they are concerned especially in the phagocytosis of the parasites, and are frequently observed to contain pigment derived from these (Plate XIII, Fig. 1, p. 380). An increase of these cells has been noted in "sympathetic ophthalmia" or panophthalmitis, *i.e.*, an inflammation started by a lesion in one eye and spreading after a variable interval to the other eye. A monocytosis has also been produced experimentally by the inoculation of rabbits and guineapigs with *Bacterium* (or *Listerella*) *monocytogenes*, which may cause disease spontaneously in sheep, gerbilles, and occasionally in man (p. 1001).

4. **Eosinophilia.** As a general rule, the number of eosinophils in the circulating blood is **diminished** in most inflammatory and septicæmic diseases. Thus, in pneumonia, they are either extremely scanty, or they may entirely disappear from the peripheral circulation during the course of the fever, their reappearance at or after the crisis being usually regarded as a favourable phenomenon. In certain diseases, however, eosinophilia or an increase of these cells may take place, either relatively, or as part of a general increase in the number of white cells. Apart from myelogenous leukæmia, in which eosinophilia may occur, these cells are sometimes greatly **increased** in certain **parasitic diseases,** for example in trichiniasis, and infestation with some intestinal worms, such as *Ankylostoma*, *Enterobius* (*Oxyuris*), *Ascaris lumbricoides*, and in hydatid-disease (p. 400) and some other types of infestation by platyhelminthes or flat-worms (p. 383). Eosinophilia is also seen, sometimes to a remarkable decree, in many **skin-diseases,** *e.g.*, pemphigus, eczema, scleroderma, psoriasis, urticaria, etc., and in syphilitic cases exhibiting special skin-lesions. A peculiar exception to the general rule that the eosinophil leucocytes tend to be diminished in numbers during febrile leucocytosis is seen in scarlet fever, perhaps from the extensive implication of the skin in this disease. In **allergic diseases,** notably in bronchial asthma, hay-fever and urticaria, these cells may be considerably increased in the blood; and, in asthma, they may be found in large numbers in the sputum also, whilst the cells are numerous

in the exudate of some cases of so-called "mucous colitis." It is not unlikely that the eosinophilia found in the blood of some patients suffering from **tuberculosis** is an allergic phenomenon, caused perhaps by, or directed against, some foreign protein produced in these particular patients from or by the tubercle bacillus. A similar explanation may account for the fact that eosinophils are occasionally found in high proportions—as much as 80 per cent. or more of the granulocytes present—in the pleural and other exudates of such tuberculous patients.[1] This eosinophil reaction may be looked upon as a characteristic rather of the individual, *i.e.*, a susceptibility to foreign protein, than as in any way a specific character of the tuberculous disease itself. The occurrence of eosinophils in various **exudates** is described in the Chapter on Inflammation (pp. 26 to 35), and, in this connection, it is noteworthy that such local infiltrations with eosinophils, sometimes "massive" in degree, may be associated with their diminution in, or perhaps even complete disappearance from, the peripheral blood. On the other hand, an infiltration of the lungs with eosinophils sometimes occurs along with a pronounced eosinophilia in the blood and is known as "Löffler's syndrome." No very definite ratio between the number of the eosinophils in the blood and in the bone-marrow—in which tissue they are, in part at all events, produced—has as yet been made out. Thus, in some cases of pneumonia, where they have disappeared entirely from the circulating peripheral blood, they may be diminished, unchanged, or even increased in number in the marrow.[2] In **Hodgkin's disease** (p. 681) there is sometimes an eosinophilia in the early stages, but this is not constant and treatment with X-rays tends to abolish it when present.

5. **Increase of Basiphil Granular Cells** (including so-called "Mast-cells" [3]). For the significance of these cells and the suggestion that they are concerned with the production of **heparin,** see p. 599. They are *not* merely the degenerated forms of other cells, but are a definite and independent variety of cell. The only condition in which they are increased in the blood itself is chronic myeloid leukæmia (myelosis).

6. **Increase of Immature or Primitive Cells.** Normally some 1 or 2 per cent. of the leucocytes in the circulating blood are young or immature forms. It is, however, pathological to find a more pronounced increase of these, and the finding of cells of more definitely **immature** type is of much diagnostic importance. **Myelocytes** and **myeloblasts** are found circulating in conditions of myeloid leukæmia, chloroma, multiple myeloma, Addisonian or "pernicious" anæmia and secondary carcinoma involving bone-marrow, and they occur in **small** numbers in any case of pronounced polymorphonuclear leucocytosis. **Lymphoblasts** may occur in glandular fever, but are found principally in lymphatic leukæmia. **Monoblasts** are distinguished from lymphoblasts only with considerable difficulty and it is probable that the larger mononuclear cells circulating in cases of glandular fever are in reality examples of this monoblast or primitive-monocyte type of cell.

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[1] "Eosinophilia in Tuberculosis," by A. M. Gill, London, *Brit. Med. Jour.*, 1940, ii, 220.

[2] Carnegie Dickson, "The Bone-Marrow," *loc. cit.*, Appendix II.

[3] If, as now seems to have been proved by Sabin and her co-workers, by methods of supravital staining, these basiphil cells are *not* degenerated forms of other cells as was originally thought by Ehrlich, his term "mast-cell" for them should now be discarded, as it means a "*fattened-up*" and hence a *degenerated* cell. With regard to the correct spelling of the word "basiphil," see footnotes to pp. 5 and 10.

SECTION IV

SPECIAL PATHOLOGY OF THE BLOOD AND BLOOD-FORMING ORGANS

Many of the more important conditions associated with pathological alterations in the blood are recognised to be the results of certain reactions on the part of the hæmopoietic or blood-forming tissues, produced by the action of various toxic substances of known or unknown origin—for example, the toxins of bacteria, animal parasites, etc., and also, it is supposed, certain poisons generated by perverted metabolic processes within the tissues and organs of the patient himself. In this connection it is important to remember that, not only for the production of the blood-cells of both the red and the white series, but also more especially for their continued development and maturation, certain " factors," " principles " and " substances " are essential. Some of these, for example, the " extrinsic factor " of Castle,[1] are derived from suitable food containing them in sufficient quantity ; others, such as the " intrinsic factors," are elaborated within the body itself, in the stomach, liver and intestine : or as the hormones of the ductless glands, especially, in this connection, the thyroid : and transferred in the circulating blood to the bone-marrow, which itself also probably takes an important part in their further elaboration and utilisation.

For the satisfactory interpretation of the findings in any individual case of infective disease, two sets of processes must be considered. First, what may be regarded as the physiological reaction of the blood-forming tissues, in order to aid the body and its tissues in their fight against the infective agent, and to combat, and, if possible, to neutralise, the effects which the disease is producing on the blood considered as a whole. Secondly, the pathological or harmful effects of the poison or irritant upon the hæmopoietic tissues, producing aberrations, it may be, in the functions of these tissues, varying in nature and in degree, or perhaps even causing their widespread destruction. Other disorders of the blood and blood-forming organs are of the nature of deficiency-diseases. The anæmias are disorders in which the erythroblastic functions of the marrow are overstrained : or are not fully developed, imperfect, or inadequate to meet the demands made upon this tissue by excessive and increasing blood-destruction. In **Addisonian** (or " **pernicious** ") **anæmia** (p. 646), the hæmopoietic functions of the marrow, though active or even up to a point actually increased in amount, are also perverted, and the normal processes of maturation of the cells of the erythroblastic series are arrested. Evidence of these phenomena is seen in the presence of macroblasts (or primitive erythroblasts) and megaloblasts in the marrow and blood, and is indicated by the abnormally large or megalocytic, or, as it is now usually termed, simply " **macrocytic,** " character of many of the red corpuscles entering the circulating blood—in other words, the production of a **macrocytic anæmia.**

In the **leukæmias,** there is some factor of unknown nature, the presence—or perhaps the absence—of which prevents the maturation of the cells of the leucoblastic series, and leads to the production in the blood-forming tissues of enormous numbers of immature or otherwise aberrant white cells. Thus, in the consideration of any of what used to be called " primary diseases of the blood," it is always possible to refer the abnormal phenomena found in the blood itself to some antecedent pathological process in the hæmopoietic tissues. Where a definite cause of this antecedent process has been discovered, *e.g.*, the presence of some parasitic or bacterial infection, neoplasm, etc., the blood-condition is usually spoken of as " secondary " ; whilst, if no such cause has yet been discovered, the disease is sometimes classified as a " primary " disorder of the blood and blood-forming tissues. In this connection it is, of course, obvious that, as our knowledge increases, all such morbid conditions of the blood will in time be proved to be " secondary," *i.e.*, due to some definite ascertainable cause acting upon the specific cells of the blood-forming organs and tissues and upon the reticulo-endothelial system throughout the body (*see* note upon the " Reticuloses and Reticulo-Endothelioses " on pp. 1262–4 of Appendix at end of book).

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[1] *See also* p. 647 *et seq.*

THE LEUKÆMIAS OR LEUCOCYTHÆMIAS

(THE LEUCOSES or PRIMARY HÆMIC MEDULLARY RETICULOSES)

Leukæmia or **leucocythæmia** is a disorder, or rather a group of disorders, of unknown origin [1], characterised by an increase—often to an enormous degree—of the leucocytes and their predecessors in the blood-forming organs, as well as in the blood, and usually also with the presence of aberrant types of blood-cell : manifesting also certain clinical symptoms such as progressive weakness, wasting, hæmorrhages from the nasal and other mucous membranes, and pronounced pathological changes in certain organs and tissues.

The disease was described by Hughes Bennett, of Edinburgh, in 1841, as " leucocythæmia " or " a condition of the blood resembling suppuration," this " pyoid " appearance of the blood being accompanied by enlargement of the liver and spleen. A few weeks later in the same year, Virchow described a case of what he called " weisses Blut " or " Leukæmia," and he distinguished clearly between this condition and true pyæmia, emphasising the presence of the characteristic pathological changes in certain of the hæmopoietic tissues. Later, Virchow divided the cases into **splenic** and **lymphatic** varieties, the bone-marrow at that time not having been recognised as a leucocyte-producing tissue. In 1879 and 1880, Ehrlich's discoveries in connection with the bone-marrow and the types of blood-cells originating in it led to the classification of these diseases into :—

(*a*) **Myeloid** or **Myelogenous Leukæmia** (**Spleno-Medullary Leucocythæmia** or **Myelocythæmia**).

(*b*) **Lymphatic Leukæmia** (or **Lymphocythæmia**).

And to these may now be added a third variety :—

(*c*) **Monocytic Leukæmia** (*with*, but apparently in some instances *without*, involvement of the **Reticulo-Endothelial System**).

Much research has been carried out since these earlier investigations, but it will simplify our conception of the whole group if we focus our attention upon the processes at work in the hæmopoietic tissues in which they originate—the **bone-marrow,** the **lymphadenoid tissues**, and the **reticulo-endothelial tissues** of the body—rather than upon the secondary changes in the blood, which should be regarded merely as symptomatic, *i.e.*, resulting from the changes and processes going on in these blood-forming tissues. Further, in all three of the main groups mentioned above, individual cases may be rapid or slow in their development and course, and can therefore be subdivided into **acute** and **chronic** varieties of each of these three main types. Moreover, certain irregular and atypical forms occur, as well as cases which appear to be more or less intermediate between the leukæmias and diseases such as chloroma and sarcoma, as well as leukæmias in which the usual blood-picture is absent (pseudoleukæmia—the so-called "*Leukämie ohne Leukämie*" of some German writers). In the rare form known as *eosinophil leukœmia,* the spleen and liver are enlarged and the bone-marrow involved ; but the cells, present in large numbers in the blood, tend to be more or less mature eosinophil leucocytes. In most cases of leukæmia, of whatever type, there is interference with, and a diminution of, the erythroblastic functions of the marrow, this diminished activity leading to the supervention of a secondary and gradually progressive anæmia from the "crowding out" of the erythroblastic tissue and its cells. In certain comparatively rare instances, however, the erythroblastic tissue of the marrow participates in the hyperplastic activities, and the result is a disorder or dyscrasia of the bone-marrow which combines the phenomena of leukæmia and erythræmia in the condition known as **erythroleukæmia** (pp. 638–9). In this combined proliferative disorder it is, however, more usual for the leukæmic change to become implanted upon a preceding erythræmia, with its characteristic erythroblastic state of the bone-marrow. We shall content ourselves with the description of the two main recognised types mentioned above, together with a short account of monocytic leukæmia, a condition now recognised as a clinical entity.

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[1] Since the above was written, considerable evidence has accumulated to show that certain of the leukæmia-like diseases of the lower animals, notably **in fowls,** are caused **by filter-passing organisms** (*see* pp. 123 and 288); but further research is required before any definite pronouncement can be made as to a similar or analogous causation of the leukæmia-group of diseases in man, though the possibility of this appears to be by no means unlikely.

1. MYELOID or MYELOGENOUS LEUKÆMIA

(Spleno-Medullary Leucocythæmia or Myelocythæmia)

(MYELOSIS, Acute and Chronic)

The more **chronic** forms of **myeloid leukæmia** are the commonest type of the disease, and last usually from two to five years. **Acute myeloid** cases also occur, and are rather commoner than are the next in order of frequency, viz., the chronic cases of lymphatic leukæmia (of which acute forms are rare).

The **ætiology** of the disease is still unknown.[1] Age and sex have a predisposing influence upon its incidence, the condition being commoner in males, especially during middle age ; but, according to case-records, heredity has little to do with its occurrence. Trauma, malaria, pregnancy, rickets, influenza, syphilis, tuberculosis, and many other conditions have, in individual cases, but with little supporting evidence, been alleged as predisposing causes ; whilst some writers regard the disease as a specific reaction of the blood-forming organs to some unknown infective or toxic agent.[1] Many, however, hold that it is to be regarded rather as a primary neoplastic disease of the hæmopoietic organs and tissues. We ourselves have already suggested above (p. 624, and *cf.* p. 647) that, on the analogy of the lack of the "extrinsic" and "intrinsic principles" in Addisonian anæmia, there may also be the possibility of a similar explanation of the causation of the leukæmias—from the **deficiency** or **absence of some as yet undiscovered "factor"** or **"factors,"** with, as a consequence, the **non-maturation** of the cells of the white-cell series. Indeed, with or without the possibility of the presence of a neoplastic process, the question of the absence of some such maturation-factor is a matter which calls for further investigation.

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[1] *See* footnote on p. 625.

Pathological Changes in the Blood. The colour of the blood may be little altered, or it may be distinctly paler than normal. It may, especially in the later stages of the disease, become more watery in consistence, owing to the associated anæmia; and coagulation is usually delayed—sometimes greatly so.

The white cells are enormously increased in numbers, *e.g.*, from 100,000 or 200,000 in cases of moderate degree, up to 500,000 or even 750,000 or more in severe cases. They vary from time to time during the course of the disease, and even at different periods of the day; whilst temporary remissions and relapses are of frequent occurrence. A fall in the leucocyte-count is often observed just before death, and a similar fall may occur from the supervention of some intercurrent acute disease such as pneumonia. The varieties of white cells especially increased are those of the granular series, *i.e.*, (i) the polymorphonuclear neutrophil leucocytes, the marrow-cells from which they are derived (the non-granular myeloblasts, and the promyelocytes [1] or cells still in process of developing their cytoplasmic granules), and the myelocytes or cells intermediate between these and the polymorphs themselves; (ii) the coarsely granular eosinophil cells, and (iii) the basiphils (sometimes still, though erroneously, called "mast-cells"). Myelocytes corresponding to the eosinophil and basiphil series also occur. Lymphocyte-like cells may be increased sometimes in absolute, but not in relative, numbers. (Plate XV, p. 596, Fig. 3.)

The relative numbers of the mature and of the immature members of the neutrophil series vary considerably in different "**chronic**" cases, and also during the course of the disease in individual patients, both treated and untreated. All forms, from the non-granular myeloblasts (Fig. 373, p. 620) and the promyelocytes beginning to show granules, and the granular myelocytes—through the intermediate myelocytes (metamyelocytes) and immature polymorph cells—down to the fully developed or mature polymorphonuclear leucocyte, are found. The earlier members of the series—the promyelocytes and myelocytes—may account for some 30 per cent. of the white cells present, though in some cases they may be more numerous. They may number as many as 100,000 or more per c.mm., and, as they increase, the maturer polymorphs—usually about 50 per cent. of the total leucocytes present—may correspondingly diminish in numbers.

In the more **acute forms** of myeloid leukæmia, and in the **acute exacerbations** which sometimes supervene in the course of chronic cases, progressively less and less mature cells of the developmental series (Fig. 373, p. 620) find their way into the blood, and, in the most acute cases of all, practically only the primitive non-granular **myeloblasts** are found, giving what at first sight looks like a large-mononuclear cell-picture. The total number of the white cells in acute myeloid leukæmia is usually not so large as in the chronic form of the disease and may be 25,000 to 50,000, or more rarely 100,000 or more. On careful study, however, the nuclear type is seen to be that of the myelocyte- and promyelocyte- series. By the peroxidase staining-reaction (p. 620) the oxidase-granules in the cytoplasm of the granular series of cells beginning to develop in the myeloblasts, or found in any granular myelocytes that may be present, can be identified. The most difficult cases are those in which only the most primitive cells of the series are present and do not yet show any cytoplasmic granules, either neutrophil or oxidase-positive. The supravital staining-methods advocated by Sabin and her co-workers are useful in differentiating the varieties of blood-cells in the leukæmias,[1] and may help in the diagnosis of a difficult case.

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[1] These have sometimes been called "*pre*-myelocytes," a hybrid for the introduction of which the present writer (W. E. C. D.) confesses himself guilty many years ago! It should, of course, have been "*pro*-myelocyte," a word used to denote the immediate predecessor of a myelocyte, *i.e.*, a cell intermediate between a myeloblast and a myelocyte.

One of the most notable features of myelocythæmic blood is the large number of eosinophil cells which are often present, *e.g.*, 5 or 10 per cent. being quite a usual number. A considerable proportion of them may be eosinophil myelocytes, characterised by their larger size and single rounded nucleus. These latter cells, however, are only very rarely as numerous as the neutrophil myelocytes. The increase in basiphil cells is a very constant phenomenon, and is more marked in this than in any other known disease—counts of 30, and even 40, per cent. having been recorded in some cases. It will be noted that these figures, being percentages of what is often an enormous total leucocyte-count, represent very considerable absolute numbers for the individual types of cells mentioned, and it is particularly in cases such as these that the leucocyte-picture becomes more instructive if the figures for the different types of cells are stated in absolute, as well as in relative, terms, *i.e.*, the absolute number of each type of cell per c.mm. compared with the normal as well as with the percentage number of the cells of each type present. Indeed, for the proper understanding and interpretation of any blood-count, the figures should be stated in absolute as well as in relative percentage numbers.

The red corpuscles, often at first not seriously affected, become progressively decreased in numbers as the disease advances. This decrease may, however, be comparatively slight in moderately advanced cases, *e.g.*, to 3,000,000, or in more advanced cases perhaps to 2,000,000 per c.mm. In patients nearing the fatal termination of the illness, the number may be even under 1,000,000, and in rare instances the white cells have been recorded as even outnumbering the red corpuscles. The hæmoglobin is diminished often not strictly proportionately, so that there may be slight increase in the colour-index to unity, or even slightly above it, the figures ranging as a rule between 0·7 and 1·2. Nucleated red cells are frequently seen in considerable numbers, especially when the anæmia is severe. In severe cases and especially towards the fatal termination, primitive erythroblasts and even hæmoglobinised megaloblasts (pp. 592 and 595) may be found in considerable numbers in the blood ; and, in the later stages of the disease, alterations in shape (poikilocytosis) and size (anisocytosis), and various degenerative phenomena such as fragmentation of the nucleus, are present.

Blood-platelets are often increased in number, especially in the earlier stages of the disease, and even considerable fragments of the megakaryocytes (Fig. 361, p. 601) can sometimes be identified in blood-films.

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[1] Whitby and Britton's " Disorders of the Blood," 4th Ed., 1942, pp. 523–527 and *ibid.*, Plate VIII (p. 525).

Changes in the Organs and Tissues :—

Bone-marrow. The change in the bone-marrow is essentially a leucoblastic reaction, with increased production of the granular series of white cells, neutrophil, eosinophil, and basiphil, but with varying degrees of failure of these cells to undergo normal maturation. The activity of the red or hæmopoietic marrow is enormously increased, and the fatty marrow is completely transformed into active blood-forming tissue. To the naked eye, the marrow, owing to the numbers of white cells present, presents a pale, homogeneous, thick fluid creamy appearance, resembling pus—the so-called "pyoid" or "puriform" marrow, the colour varying—usually yellowish, sometimes pinkish-yellow, and occasionally greenish-yellow. In old-standing cases, especially in elderly patients, atrophic and degenerative changes tend to supervene, and most of the active marrow gradually becomes transformed into inert, translucent, gelatinous or mucinoid material, which may be pale yellow to dark red in colour, or may, in some cases, present a patchy mixture of these. **On microscopical examination,** the marrow from a typical case shows an enormous increase in especially the neutrophil myelocytes, but also in eosinophil and basiphil cells. In freshly prepared films, evidence of this active proliferation is shown also by the presence of numerous mitotic figures in these cells. Along with this increase in granular white cells, a corresponding decrease or atrophy, sometimes after a preliminary transient increase, occurs in the erythroblastic elements, some of which, as noted above, may pass into the blood-stream while still nucleated. Large blood-destructive phagocytic cells (*cf.* Plate XVII, p. 616) are usually present in great numbers. The fat-cells are much diminished, and may entirely disappear. The megakaryocytes, or mononucleated giant-cells, though often smaller in size than normal, are frequently increased in number, and, as already noted (p. 628 and Fig. 361, p. 601), in addition to giving rise to the platelets, which may be abnormal in both number and size, fragments of the cytoplasm of these cells may break off and be found in the circulating blood.

Spleen. This organ is almost invariably enlarged—as a rule, greatly so, especially in the more chronic cases. It usually maintains a comparatively normal shape, the notches being distinct, and it may weigh from 5 to 8 lb., or even, in some cases, much more ; whilst it may come to measure 8 or 10 or even over 20 in. in length, its lower extremity (unless anchored by previous adhesions or by an abnormally developed costo-colic fold of peritoneum, in which case the enlargement may take place upward), passing downwards and to the right, and coming to lie in the right iliac fossa. It may press upon the right ureter and cause hydronephrosis. The capsule of the organ may be thickened, often irregularly, from recurrent attacks of perisplenitis ; and there are, frequently, adhesions to surrounding structures. The spleen is firm and hard, and usually presents on its surface a number of large, yellowish-white, homogeneous, necrotic areas of infarction, produced probably by thrombosis. Older infarcts, showing partial or complete absorption, may occur. On section, the spleen-tissue—unless softened by terminal septic infection—is smooth, and somewhat dry and firm, its colour varying in different cases, but being most commonly of a homogeneous pinkish or pale red tint ; and the Malpighian bodies are obscured and cannot usually be distinguished.

Microscopically, the changes in the enlarged spleen vary considerably in different cases and at different stages of the disease. In the early stages, there is considerable increase in the cellular content; whilst later, various degenerative processes, especially fibrous overgrowth of the reticulum, supervene, both in the Malpighian bodies and in the pulp. In the latter, there are, usually, pronounced proliferation and phagocytic activity on the part of the endothelial cells lining the sinuses. Some of these cells may attain large dimensions, and frequently show great increase in their normal functions of destroying effete red corpuscles, as well as members of the abnormally increased leucocyte-series. The pulp and its sinuses sometimes contain nucleated red cells in proportions in excess of those present in the circulating blood. There is no evidence that this excess is due to any local formation of these cells, and it is more likely that they have been sifted or filtered out from the blood, preparatory to their destruction by the phagocytic cells. It is probable that the myelocytes, also present in considerable numbers, are similarly in process of destruction. In the spleen, there is thus hyperplasia and increased activity of its pulp-cells, an accumulation and destruction of the abnormal blood-cells, and a progressive atrophy and fibrosis of its component tissues. The conditions in this organ are, therefore, to be regarded as effects, rather than as a cause, of the disease, the spleen acting as a filter and destroying the abnormal blood-cells. Under X-ray treatment, temporary diminution in the size of the organ may be produced.

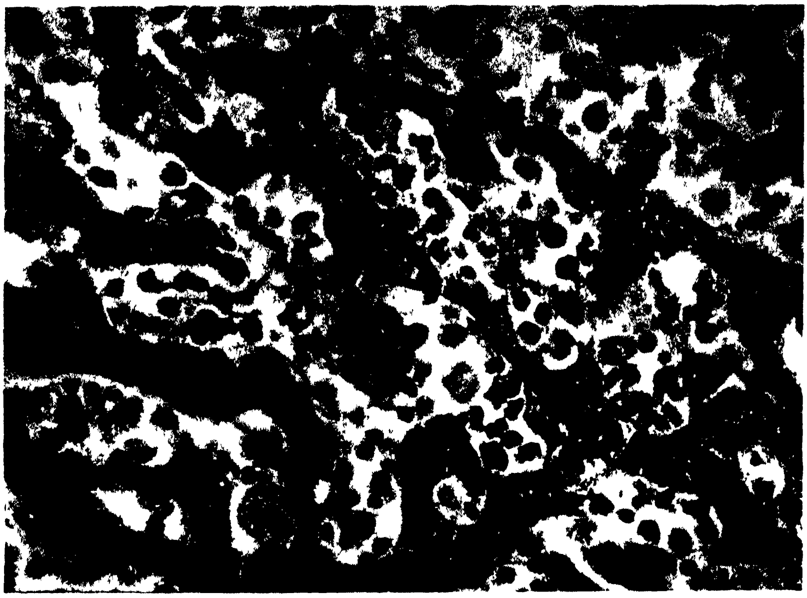

FIG. 374. *Liver in Myeloid Leukæmia.* Large numbers of cells, chiefly myelocytes, are seen between the columns of liver-cells—mostly within the capillaries. × 400.

Liver. This organ is usually increased in size, but not, as a general rule, to such an extent as in lymphocythæmia. It is pale in colour, the capillaries between the columns of liver-cells, and also the connective-tissue framework, *e.g.*, of the portal tracts, being crowded with granular myelocytes and polymorphs, many of the latter immature (Fig. 374). These have usually been regarded as an "infiltration" or mechanical sifting-out and lodgment of increasing numbers of such cells from the circulating blood ; but some recent observers believe that actual proliferation by mitotic division does occur *in situ*, and that there is a return to the hæmopoietic activity exhibited by the liver during fœtal life. Occasionally, localised tumour-like nodules of such cells occur.

Lymph-nodes. These do not, as a rule, exhibit any pronounced general enlargement in this variety of leukæmia, but there is usually a certain degree of hyperplasia, more especially of the phagocytic endothelial cells lining the lymph-sinuses.

Kidneys. These organs are usually enlarged, pale, and often fatty. Microscopically, their capillaries and connective-tissue framework, *e.g.*, between the tubules, are crowded with myelocytes. Similar accumulation of these cells may also be seen in the capillaries of the **lungs, heart-muscle,** and elsewhere.

Hæmorrhages, especially from mucous membranes, are frequent. Death may result, in such cases, from large cerebral hæmorrhages or from hæmorrhage into the lungs ; but extravasation of blood into other internal organs is not so common as in lymphocythæmia. Fig. 500 on p. 861 illustrates numerous small hæmorrhages in the kidney.

2. LYMPHATIC LEUKÆMIA or LYMPHOCYTHÆMIA (LYMPHADENOSIS, Acute and Chronic)

Of **lymphatic leukæmia,** there are, as in the myeloid type, both acute and chronic forms, corresponding with the degree of maturation of the variety of white cell involved. The **chronic** form of lymphatic leukæmia corresponds with the appearance in the blood of great numbers of **small lymphocytes,** regarded by most writers as the mature cells of the lymphocyte-series. In the more **acute** forms, either acute from the start, or an acute exacerbation supervening in the course of the chronic disease, and especially towards its fatal termination, the **larger lymphocytes** are present in the circulating blood, and, in the most acute and rapid cases of all, **lymphoblasts,** with the production of a **lymphoblastic leukæmia.** This is much rarer than the chronic type. The latter affects especially adults between forty-five and sixty, males oftener than females. Acute lymphoblastic leukæmia, on the other hand, is a disease almost exclusively of children and young persons ; although, as already indicated, exacerbations in chronic cases may be characterised by reversion to the less mature cells of the lymphocyte-series.

The case-incidence of these types of leukæmia varies in different recorded series, and is difficult of accurate assessment, owing, in the past, to considerable uncertainty in differentiating the more primitive types of cell from one another—lymphoblast from the non-granular myeloblast, and both of these from the primitive cell of the monocyte-series—the monoblast (*see below* and pp. 634–5). Their relative proportions may, however, be stated approximately as : chronic myeloid, 3 cases ; acute myeloid, 2 cases ; and chronic lymphatic, 1 case ; whilst the acute lymphatic variety is very much rarer than the other three.

This acute lymphoblastic type is rapidly fatal and runs a course of perhaps only a week, though more commonly it lasts some five or six weeks. The **lymphoblasts** are large mononuclear cells, the cytoplasm of which is peroxidase-negative (*see* p. 620), and also does not contain any azurophil granules. The numbers of these primitive cells in the blood are variable, perhaps 50,000 to 75,000 per c.mm., sometimes less, but frequently up to half a million or more. The relative numbers of the cells of the lymphocyte-series may exceed 90 per cent. of the white cells, and reach even 98 or 99 per cent.

In **chronic lymphatic leukæmia,** the small lymphocyte is increased in the blood in numbers usually not exceeding about 100,000, though, occasionally, much higher numbers are found. These small lymphocytes may constitute some 85 to 95 per cent. or more of the total leucocyte-count. Varying admixtures with large lymphocytes are found in individual cases, along with an occasional lymphoblast, and, as already noted, these cells increase during acute exacerbations, and especially towards the fatal termination. Fig. 4 of Plate XV (opposite p. 596) illustrates a blood-film from a case of chronic lymphatic leukæmia during such an exacerbation, with the presence of larger, in addition to the smaller, lymphocytes, some of these larger cells being probably lymphoblasts. This film also illustrates the diminution in numbers of the neutrophil polymorphs and other granular cells, as well as the occurrence of occasional nucleated red cells, usually normoblasts. A study of the various films illustrated in this coloured plate will enable the reader to follow the descriptions of the blood in the two main types of leukæmia, and these may also be contrasted with the appearances depicted in the film of a polymorphonuclear leucocytosis in Fig. 2 of the plate.

The **red corpuscles** are affected in much the same way as in myeloid leukæmia, but usually only at a later period, when the infiltration of the bone-marrow with cells of the lymphocyte-series has become pronounced. Nucleated forms in the blood are generally few in number or even absent until, at all events, comparatively late in the course of the disease, those found being chiefly normoblasts. They may, as in any profound anæmia, begin to appear in the peripheral circulation when the erythrocytes have become reduced to less than half their normal numbers.

Blood-Platelets tend to be diminished in number in this variety of leukæmia rather than increased as in myelocythæmia. This diminution corresponds to a diminution in the number and size of the **megakaryocytes** (Fig. 361, p. 601) in the marrow. In some cases, the platelets completely disappear from the blood, and purpuric hæmorrhages then tend to occur.

The **Bone-Marrow,** especially later in the course of the disease, usually shows great " infiltration " with lymphocyte-like cells, and a corresponding diminution, or even, in large areas, a disappearance of the other elements normally present. This form of lymphocythæmic change is often extremely irregular in its distribution, and may, as anæmia supervenes, be mixed with a certain amount of erythroblastic reaction, giving a characteristic patchy red-and-white appearance to the marrow. Degenerative changes supervene later. As to the nature of these lymphocyte-like cells, opinions vary greatly. Some regard them as an infiltration of the tissue by cells produced elsewhere, *e.g.*, in the lymph-nodes ; but opponents of this theory point out that the marrow is often extensively affected in cases where these nodes show little or no change. Lately, the view that these cells are, in reality, earlier members of the myelocyte-series, has gained ground, and it is believed that the lymphoblasts or primitive lymphocyte-like cells, especially the larger varieties, are simply non-granular promyelocytes and myelocytes, *i.e.*, myelocytes in which the granules have not yet developed, or that the two series of cells have a primitive common ancestral cell. In some cases of myeloid leukæmia, many of the myelocytes may be extremely poor in granules, and some may have none distinguishable, in which case the cell closely resembles the " large lymphocyte " of lymphatic leukæmia. Differential staining by the peroxidase and supravital methods may, however, serve to differentiate some of these doubtful cases from one another, and also from those cases thought to be monocytic and monoblastic (*see below*, p. 634).

Spleen. The degree of enlargement of the spleen varies considerably, and in chronic cases the organ may attain a size comparable with that seen in the myeloid type, the amount of enlargement depending upon the duration of the illness. Its pulp is crowded with the lymphocyte-like cells and, in some cases, the Malpighian bodies are enlarged and hyperplastic, sometimes in marked degree.

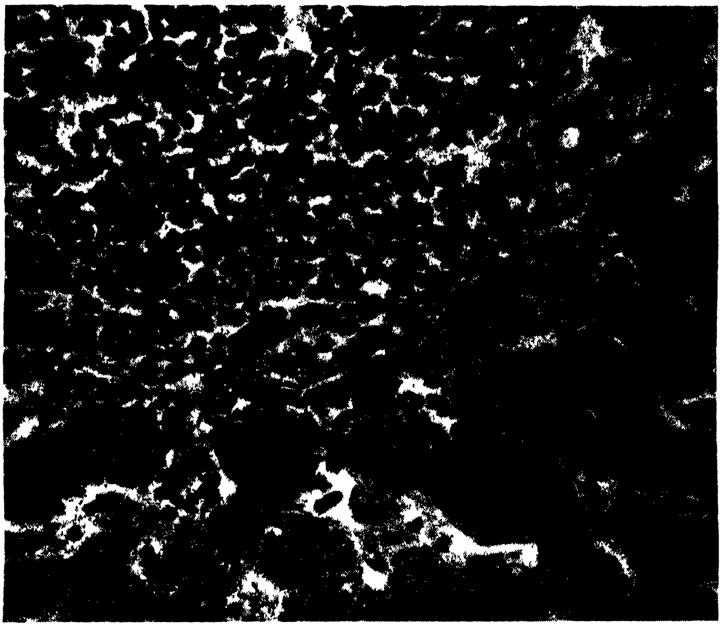

FIG. 375. *Liver in Lymphatic Leukæmia*, showing the infiltration with small " lymphocytes." Hæmatoxylin and eosin. ×360.

Lymph-Nodes. In many cases widespread enlargement supervenes early in the course of the disease, or the enlargement may affect only one or more groups of nodes, especially the cervical, and also the axillary, the inguinal, the prevertebral, or the mesenteric. In several cases observed by one of us, the nodes at the hilum of the liver especially have been affected. More commonly, two or more of these groups are involved. In other instances, the glandular enlargement is not a marked feature of the disease. The localisation to special groups of lymph-nodes is seen usually only in the more acute cases, and the tumour-like masses may resemble a lymphosarcoma in both its naked eye and microscopical appearances. This variability in the pathological condition of the lymph-nodes suggests the probability that, in reality, such cases comprise a group of allied diseases, in some of which the condition is, apparently, primary in lymphadenoid tissue ; in others, in the bone-marrow ; whilst, in a third variety, both of these structures are affected.

The **Liver** and the **Kidneys** are often enlarged—more so than in the myelogenous type—there being sometimes great " infiltration " of the tissues with lymphocytes, or even the appearance of irregular nodules and masses of adenoid tissue resembling tumour-growth. Such organs may exhibit a uniform dead-white appearance, but often white lines of " infiltration " may be seen along the blood-vessels and in the connective-tissue framework. Other organs, *e.g.*, the **heart** and **lungs**, may also show analogous changes.

Multiple **hæmorrhages** are common, especially in the more acute forms of the disease, but they are, as a rule, not so profuse as in the myelogenous type. Often widely scattered, they may be found, for example, in the brain, retina, skin, kidneys and enlarged lymph-nodes, etc. When the **anæmia** becomes pronounced, fatty change, in varying degree, is found in the organs.

3. MONOCYTIC LEUKÆMIA

Originally, this condition was thought to represent merely a temporary phase in the course of cases of myelogenous leukæmia, the large monocytes present closely resembling myeloblasts ; and there has recently been a tendency amongst some writers on the subject to revert to this view, although others consider that such cases should be recognised as constituting a distinct clinical entity. In the cases recorded by those who take the latter view, there has often been an associated infection of the mouth or throat with the fusi-spirochætal organisms of Vincent's angina (pp. 374 and 710), ulceration taking place in most of the cases. Fever has been common, and, though remissions associated with a return of the blood-picture towards the normal have occurred, the disease has been uniformly fatal.

The blood in such cases has shown an anæmia of moderate severity, and, though there has usually been an increase of leucocytes to 25,000 or 50,000, " aleukæmic " forms have been described in which the total leucocyte-count has been less than 1,000 per c.mm.

In the active stages of the disease, in some of the cases described in the literature, 50 to 95 per cent. of the white cells present in the peripheral blood were said to be " monocytes " with typical horseshoe-shaped nuclei ; but, ultimately, more primitive cells were observed, and these, which very closely resembled myeloblasts, gave rise to considerable difficulty in making the differential diagnosis. Since the onset of the disease was insidious and in some cases associated with two or more remissions, the length of the illness was variable, but the total duration was seldom more than a few months.

The lymph-nodes showed proliferation of their reticular structure, and were packed densely with monocytes. Monocytic infiltration, sometimes accompanied by myelocytes and myeloblasts, was said also to occur in the liver, bone-marrow and spleen, and there might be focal infiltrations in the rectum, colon or appendix, together with necrotic changes.

As opinion still differs widely upon the existence of this variety of leukæmia as a separate entity, and as we ourselves have had but limited experience of it, we give the above account of it under reserve. Campbell, Henderson and Croom, of Edinburgh, working in the laboratory of one of the authors (A. M. D.), have investigated two cases which they describe as " monocytic leukæmia with myeloid hyperplasia and localised tumour-formation," [1] and they suggest that, in individual cases of " monocytic leukæmia " recorded by different authors, the varying phenomena described might conceivably be interpreted as (1) those of a primary leukæmic proliferation either of the monocytic or of the myelocytic series of blood-forming cells, with a secondary reaction on the part of the other member of the pair: (2) that the " leukæmic stimulus," whatever its nature may be, affects the two separate cell-series, monocytes and myelocytes together: or (3) that there may be hyperplasia of a primitive parent- or stem-cell with simultaneous differentiation into the two distinct daughter-types, monocytic and myelocytic. These writers are inclined to consider the third of these suggestions as most in conformity with the findings in their own particular examples. In these, they did not find any evidence of the reticulo-endotheliosis described as occurring in some of the recorded cases of monocytic leukæmia, and they consider that the various individual cases have been characterised by correspondingly varying degrees of such endotheliosis on the one hand, and the hyperplastic formation of blood-cells (monoblasts or monocytes, lymphoblasts or lymphocytes, and granulocytic myeloblasts or granulocytes) on the other—or by a varying admixture of endotheliosis and leucoblastic activity of the types enumerated. We realise the difficulty of distinguishing the " monoblast " from the " non-granular myeloblast " and we await with interest the results of further investigation of the problem.

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[1] *Jour. Path. and Bact.*, 1936, **42**, 617–634.

4. ATYPICAL LEUKÆMIA

In addition to the above " monocytic " type of leukæmia recognised by some writers, other instances also occur from time to time in which, in spite of clinical similarities, the blood-picture does not accord with that of any of the ordinary forms of myeloid, lymphatic, or " monocytic " leukæmia.

" **Aleukæmic leukæmia** " (or " **aleukæmic myelosis** ") is a condition in which, in spite of the presence of the typical lesions or proliferative reactions in the hæmopoietic and other organs and tissues characteristic of leukæmia, myeloid or lymphoid (and also, perhaps, " monocytic "), there is *not* a corresponding leukæmic increase of the white cells in the blood itself—hence the term " aleukæmic "—and there may even be a diminution in their total number. Some of the cells characteristic of the myeloid or of the lymphoid type of the disease may, however, be found, and constitute a varying proportion of the leucocytes present; but, in certain cases, even this aid to the diagnosis may be absent, and then only a biopsy of the sternal bone-marrow will serve to establish the true nature of the disease, which may otherwise be mistaken for some indefinite condition such as " aplastic anæmia." Some of these puzzling cases, however, terminate with all the usual phenomena of a leukæmia, perhaps most frequently of myeloid type.

In cases of doubt, where enlargement of the spleen co-exists with any blood-changes, assistance may, as just suggested, be obtained by biopsy of the sternal bone-marrow (" sternal puncture," p. 603 *et seq.*).

Cases of **eosinophilic leukæmia** have also been described, and, though in certain instances there is some doubt as to the condition being other than a modification of a myelogenous type of the disease, in others there is considerable evidence for regarding the condition as a separate entity.

Leukanæmia is a term which has been introduced to describe conditions in which the blood-picture resembles that of Addisonian anæmia, but combined with leukæmic characters. There is, however, at present no obvious reason for considering these cases as separate clinical entities.

Leukosarcoma was first described by Sternberg in 1915, and represents the type of case in which blood-changes resembling those of lymphatic leukæmia are found in association with enlargement of one group of lymphatic nodes, which in themselves appear to be the seat of lymphosarcomatous changes.

It has been suggested that these cases represent the late results of irradiation of lymphosarcomatous masses and that the condition is, again, not to be regarded as a separate clinical entity. We have ourselves, however, seen cases of this description in patients who had not been submitted to any X-ray treatment (pp. 633–4, and *cf.* footnotes on pp. 288 and 625).

As mentioned above, there is much support for the view that all of these diseases are genetically related ; and that they may be but different aspects of **neoplasia** of the **hæmopoietic tissues.** Under this view, the atypical blood-cells in leukæmia may be thought of as " free-swimming " sarcoma-cells. This view rationalises the inter-grading between lymphosarcoma without leukæmic manifestations, leukæmia with extensive infiltrations and what in some instances appears to be local or sometimes widespread neoplastic proliferation in various organs and tissues, and leukæmia proper.

5. CHLOROMA

(Chloroleukæmia)

This condition is now regarded as a rare type of leukæmia, for the blood-changes are those of an acute myeloblastic leukæmia, and the disease is fatal in from six to eight weeks. Lymphoid types also have been described, but, since lymphoblasts and primitive myeloblasts are distinguished with such difficulty, it is more than probable that all the cases are in reality of myelogenous origin. Greenish-coloured tumours, usually subperiosteal in situation, are present in the bones of the skull, especially in connection with the orbits (G. H. Melville Dunlop, 1902), and the thorax and over the long bones (pp. 222, 319 and 1231). The bone-marrow is also affected and shows similar greenish deposits and infiltrations. The greenish colour disappears on exposure to the air (p. 321). The lymph-nodes and spleen are usually, but not always, enlarged. The chloroma-cells which infiltrate the tissues appear to be of the same type as those circulating in the blood.

6. MYCOSIS FUNGOIDES

Like chloroma, **mycosis fungoides** is related to this group as a hæmopoietic disease which may have a leukæmic aspect. It is a skin-condition in which, after a period of pruritus, firm, elevated reddish tumours (" tomato-sores ") develop on the surface of the body, most often on the scalp, face and trunk. Histologically, various cell-types, all capable of reference to immature or atypical elements in hæmopoiesis, compose the cutaneous masses and more diffuse infiltrations. The blood may show similar cells in large numbers. This disease must be considered a variant belonging to the general group of **leukæmia cutis.**

AGRANULOCYTOSIS

(Agranulocytic Angina : Neutropenia)

This grave disorder is characterised by the virtual disappearance of the marrow-formed granular leucocytes from the blood. Necrotic conditions, particularly of the mouth, including fusi-spirochætal infections of Vincent's-angina type (pp. 374 and 710), are usually present.

The two chief types of the disease at present recognised are distinct both as regards pathology and treatment: (1) " primary " or so-called " idiopathic ": (2) secondary.

The **primary** form affects women of middle age in particular, but may be seen also at other ages, as well as in males and occasionally in children. The extreme **neutropenia** undoubtedly precedes the ulcerating lesions, and for this reason the condition must be regarded as primarily a disease of the bone-marrow and the ulcerating lesions as secondary to the blood-changes. Two separate and distinct conditions have been noted in the bone-marrow in these cases. Sometimes there is obvious **aplasia** of the earlier cells of the myeloid or leucoblastic series ; but in other cases there are considerable numbers of the more primitive cells, *i.e.*, myeloblasts, present, and the disorder would therefore appear then to be one of **defective maturation.**

Nucleic acid and its derivatives are substances which promote the maturation of the leucoblastic cells, and the administration of these substances, particularly pentose nucleotide (" pentide " or "pentnucleotide "), to patients with a neutropenia will stimulate the delivery of mature cells into the blood-stream. If aplasia is present, these substances are ineffective. Varying degrees in the severity of the disease occur, from acute fulminating rapidly fatal cases, to those which are sub-chronic, sometimes with relapses.

The blood-picture may be one of moderate anæmia with the total leucocyte-count reduced to perhaps 1,000 cells or less per c.mm. ; and of these the polymorphs are usually less than 300 per c.mm., and in some instances they may be completely absent. In the event, therefore, of an attack of bacterial infection, general or local, *e.g.*, in the throat or elsewhere—and because of this diminished production or even entire absence of polymorphs—the occurrence both of an inflammatory leucocytosis in the blood and any efficient local emigration of leucocytes at the site of attack may thus be prevented, and the occurrence of suppuration and abscess-formation rendered impossible.

The **secondary** types of the disease result from the destructive action upon the bone-marrow of some agent such as drugs of the barbiturate class, and of the sulphonamide group, salvarsan and other arsenicals (anginous ulceration may supervene in predisposed patients who have been taking these drugs), trinitrotoluene (T.N.T.) and dinitrophenol, benzol and mustard-gas : X-rays and radium when administered in excessive doses : and the effects of severe infections such as osteomyelitis, typhoid and pneumonia.

Various types of **bacteria,** especially staphylococci and some varieties of streptococci, produce a **leucocidin,** and it has been suggested that, in the so-called " primary " type of the disease, there may be a focus of infection from which this leucocyte-destroying substance is absorbed. In the secondary type, the destructive changes may be due to the direct action of chemical or other agents on the cells in the bone-marrow ; but, on the other hand, these agents may merely render the cells more susceptible to attack by the products of organismal growth.

INFECTIOUS MONONUCLEOSIS (Glandular Fever)

(*See* p. 683.)

"**Enterogenous cyanosis**" has already been considered (p. 160). The so-called "**cyanotic types of polycythæmia**" are an indefinite group of cases amongst which is included **Ayerza's disease** (p. 482), which is associated with sclerotic changes and narrowing of the pulmonary vessels. These are examples of **secondary** polycythæmia or erythrocytosis, and therefore do not come into the primary-erythræmia group.

ERYTHROLEUCOBLASTOSIS

In infants, stillborn or dying shortly after birth, there is sometimes found both excessive hæmopoietic activity and persistence of hæmopoiesis in regions in which it would normally be found only in embryonic and early fœtal life. Wanstrom[1] (1933) described active blood-cell formation in the chorionic villi of the placenta of such a child. To this condition the terms "erythroblastosis," "leucoblastosis" and "erythroleucoblastosis" are given, according to whether red corpuscles, white cells, or both, are being produced in excess. **Congenital hydrops** or **œdema** is present, with ascites which may be so pronounced as to cause dystocia ; and also **icterus** which stains the cerebral basal ganglia, leading to the designation of "**Kernikterus**" in the German literature. This disorder shows a familial tendency in association with icterus gravis. Nothing further is known as to its ætiology.

ANÆMIA

The general term "anæmia" should, strictly speaking, be reserved for the description of a state in which the circulating blood-elements are reduced to a level below the normal either in quantity or in quality. It is, however, in practice reserved to denote a diminution in the numbers of the erythrocytes or in their contained hæmoglobin.

Since the red corpuscles are in health continually undergoing destruction, it follows that the maintenance of a normal blood-level will require a constant supply of new corpuscles to replace those destroyed, the average life of an individual corpuscle being estimated at only some two to six weeks' duration.

Hence anæmia will occur :—

1. When production and maturation of new red corpuscles in the bone-marrow is in any way deficient.
2. When loss or destruction of red corpuscles in the circulation and in the reticulo-endothelial system or elsewhere exceeds the production of new elements.

It is convenient to classify conditions of anæmia according to their **causation,** and to abandon the older and misleading division into "primary" and "secondary" types (p. 664). Thus, the types of anæmia which may be found are :—

I. **Anæmias due to failure of hæmopoiesis from nutritional, toxic and other causes**[2] (p. 642).
II. **Hæmolytic anæmias** (p. 655).
III. **Anæmias due to and following hæmorrhage** (p. 633).
IV. **Anæmias due to various other known causes** (p. 664).
V. **Anæmias of unknown causation** (p. 667).

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[1] "Erythroleucoblastosis in the Newborn," by R. C. Wanstrom, *Amer. Jour. of Path.*, 1933, **9**, 623.

[2] If the term "dys-hæmopoietic" is used in this connection it implies, not merely lack or deficiency, but also *perversion* of the process, as the Greek prefix δυσ, *dys-*, has more than the simple meaning of ἀ-privative. There is also the implication of something *bad* or *wrong*, and hence, in a pathological term, the meaning of *perverted*, like the English prefixes in *un*-happy or *mis*-taken.

Anæmias of the first group, due to **interference with,** or **failure of, hæmopoiesis,** may be subdivided into those due to **deficiency** or **absence** of certain necessary hæmopoietic factors—Addisonian or so-called "pernicious" anæmia and chlorosis being typical examples : and those of **toxic** origin, *e.g.*, due to sepsis or to poisons such as lead or arsenic ; whilst in others the **capacity** of the blood-forming cells **to proliferate** is abolished, *e.g.*, by the action of radium and X-rays.

The hæmolytic anæmias may be of infective origin (*e.g.*, malaria), or be of so-called auto-intoxication type. The latter comprises such conditions as paroxysmal hæmoglobinuria, acholuric jaundice, etc., in which there is some inherent or acquired defect of the red blood-corpuscles whereby they are rendered more susceptible than usual to destruction (pp. 586–7 and 658–9).

Certain cases of "toxic" anæmia are also of hæmolytic type, but it is more nearly correct in the majority of cases to group these under the heading of "nutritional" types, as will be explained later.

The remaining groups need no especial mention, as their designations indicate sufficiently the type of anæmia included under each.

It will now be evident why anæmia should be regarded as a **symptom** or **result** of disease rather than as a disease in itself. Indeed, apart from their infestation by parasites such as those of malaria, actual *disease* of the red corpuscles themselves as a cause of anæmia is rare.

The changes found in the circulating blood in the various forms of anæmia are essentially alterations in the **number** and **size** of the corpuscles : alterations in the **amount of hæmoglobin** contained in them : and any deficiency in the degree of their **maturation.** In regard to the **size** of the corpuscles, anæmias may be classed as macrocytic, normocytic, or microcytic : according to the degree of **maturation,** as megaloblastic and macroblastic, normoblastic, microblastic, and erythrocytic : and, according to **hæmoglobin-content,** as hypochromic, normochromic [1] or hyperchromic. Their **numbers** are reduced in varying, and sometimes in extreme, degree. Anæmias can thus be classified into the following categories :—

Size of the erythrocytes. **Hæmoglobin content.**

(1) Normocytic and normochromic with normal volume-index and normal colour-index.
(2) Normocytic and hypochromic with normal volume-index and lowered colour-index.
(3) Macrocytic and hyperchromic with increased volume-index and increased colour-index.
(4) Macrocytic and normochromic with increased volume-index and normal colour-index.
(5) Macrocytic and hypochromic with increased volume-index and lowered colour-index.
(6) Microcytic and hypochromic with lowered volume-index and lowered colour-index.

The nutritional factors in the production of anæmia have long been recognised, as it became obvious, early in hæmatological studies, that the supply of new red corpuscles demands an adequate supply of every constituent necessary for the building up of new erythrocytes. Yet for many years scant attention was paid to the exact details of these requirements, except as to an adequate supply of iron as an essential constituent of hæmoglobin. Later work has shown that the hæmopoietic system is extremely sensitive to many factors in connection with its nutritional needs, and that the problems involved extend far beyond the supply of the actual nutriment required, for there may, in certain cases, be a failure to make use of nutritional factors even when these are being supplied in fully adequate amount.

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[1] We regret having to employ hybrid words such as "normoblast" and "normochromic" in our descriptions, but they are already entrenched in the literature, and it would make confusion worse confounded if we altered them at the present moment. Perhaps Pathology, like her sister science, Anatomy, will some day undertake a "purge" of her swollen and perverted nomenclature, when hybrids and endless and unnecessary synonyms will disappear (*cf.* footnotes on pp. 5 and 661).

In brief, the hæmopoietic system demands an adequate supply of, and capacity for utilising, **iron** with traces of other metals such as **copper,** the later being probably necessary to assist in the proper absorption and utilisation of the iron : the **hæmopoietic principle, " hæmopoietin,"** resulting from the interaction of an " **extrinsic factor** " contained in the diet, with an " **intrinsic factor** " which is contained in normal gastric juice, the principle formed being **absorbed** from the intestine and **stored** in the liver : of certain **vitamins** (the anti-scorbutic vitamin C in particular) : and finally, of **internal secretions** of which thyroxin, the active principle of thyroid secretion, is the most important.

From what has been said, it will be apparent that deviations from the normal in diet, digestion, absorption and storage, as well as endocrine disturbances, will all play a part in the so-called "nutritional" abnormalities connected with anæmic states. Moreover, it must be remembered that, usually, more than one, sometimes many, factors, are at work in any given case.

In the treatment of anæmia, the administration of the anti-anæmic principle, hæmopoietin, is efficacious during the megaloblastic and earlier macroblastic stages of maturation : iron at the later macroblastic or erythroblastic, and especially at the normoblastic, stage, for example in all the hypochromic anæmias : but, in the macrocytic anæmias, only when the colour-index is much more reduced than the volume-index, *e.g.*, in No. 5 in the foregoing table.

I. ANÆMIAS DUE TO DEFECTIVE HÆMOPOIESIS

(a) GROUP DUE TO DEFICIENCIES OF CERTAIN NECESSARY FACTORS

1. CHLOROSIS

Chlorosis is a hypochromic and usually moderately microcytic anæmia which occurs almost exclusively in girls, especially just after the establishment of the menstrual function, *e.g.*, from the age of fourteen to seventeen or later, until that of twenty-four or twenty-five ; and, though the ultimate nature of the disease is still unknown, its mechanism is probably a functional insufficiency of the bone-marrow—perhaps in congenitally predisposed subjects. It is characterised especially by a relative diminution in the amount of hæmoglobin and size of the corpuscles (No. 6 in the table on p. 641) : by a moderate diminution in their number per c.mm. (p. 643) : and by the presence of some of the other ordinary symptoms of anæmia, *e.g.*, dropsy. There is, however, no special tendency to the occurrence of hæmorrhages ; and there is usually amenorrhœa.

Ætiology. Many factors may contribute to the causation of the disease, which in its most typical form has been steadily decreasing throughout the world during the last half-century. Congenital hypoplasia or defective development of the circulatory system and generative organs was thought by Virchow to have some bearing upon it. Others have thought the condition due to diminished capacity for the assimilation of iron. Intestinal auto-intoxication (copræmia) has been considered by some to be the cause, as constipation is a prominent symptom, but such constipation is probably a result rather than an ætiological factor. Certain predisposing factors in its causation have long been recognised—its occurrence in young women being undoubtedly, in many cases, due largely to the special strain upon the system entailed by the establishment of menstruation ; whilst other predisposing causes are bad food and unhealthy hygienic conditions, and perhaps heredity. Its occasional occurrence in boys was recognised by Professors W. S. Greenfield and Sir Thomas R. Fraser in Edinburgh many years ago.

The skin shows a yellowish or very slightly greenish-yellow tinge in a typical case—hence the name given to the condition.[1] The subcutaneous fat may be normal in amount or even present in excess. Such cases as occur now often show no such greenish coloration, and this is absent also in the very infrequent cases in which males appear to be suffering from the condition.

In the majority of anæmias, there is an "oligæmia," *i.e.*, the total mass of the blood is usually diminished, but in chlorosis, as demonstrated by the carbon-monoxide method of Haldane and Lorrain Smith, the total mass is usually, and often remarkably, **increased**—a fact to be borne in mind in interpreting the blood-count and estimation of hæmoglobin in this disease (pp. 594 and 642). The increase in the amount of plasma, which, according to Haldane, may be doubled in total bulk, has been regarded by some as the essential factor in the production of chlorosis, but the disease is not cured by its reduction, unless, at the same time, **iron** is administered.

The blood is distinctly pale in colour, and the most important pathological change in it is the marked diminution in the amount of hæmoglobin present, *e.g.*, to 40 per cent., 30 per cent., or even 20 per cent. ; whilst the number of erythrocytes may not be greatly below normal, *e.g.*, four-and-a-half or four millions, though in severe cases it may fall to three-and-a-half or three millions or less per c.mm. As a rule, they show only a slight to moderate degree of anisocytosis, mostly in the direction of diminution in size ; nor, except in severe cases, is there much irregularity in shape, any poikilocytosis present being due mostly to the presence of oval and not "pointed" or "tailed" forms. The characteristic feature is the pallor of their centres, from deficiency of hæmoglobin. Occasional erythroblasts, of normoblastic type, are found, especially in advanced cases, their number varying considerably from time to time even in the same case. The leucocytes may be diminished, but are more usually normal or slightly increased in numbers ; and, in a series of cases examined by one of the authors, this increase, though varying from day to day, was distinct. The platelets are increased in number. The specific gravity of the blood (which in the healthy, adolescent female, is normally just under 1·055) may fall to 1·035 or even 1·030. The alkalinity is unaltered, but the coagulability is distinctly greater than in other anæmias of equal degree—an important point in connection with the occurrence of thrombosis which has frequently been described in chlorosis (p. 589), *e.g.*, in the femoral or other veins, cerebral venous sinuses, and even, though rarely, in arteries.

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[1] Greek χλωρός, *chlōros*, greenish-yellow or pale-green. Osler said that, in such cases, "it takes the eye of faith" and "a great deal of imagination" to "see the slightest imaginable tint of olive green in the shadow beneath the chin, but that is all."

The anæmia rapidly improves on giving iron, and is practically never fatal, unless from the occurrence of venous thrombosis, or some intercurrent malady.

2. HYPOCHROMIC ANÆMIA

(Chronic Microcytic Hypochromic Anæmia)

This variety of anæmia has in the past received many names—**hypochromic anæmia** (group No. 6 in the table on p. 641) being perhaps the simplest and most convenient—but other names in common use are microcytic anæmia, simple achlorhydric anæmia, " idiopathic "[1] hypochromic anæmia, chronic chlorosis, and Witt's anæmia.

Hypochromic microcytic anæmia is associated with a low colour-index and occurs almost exclusively in middle-aged women, especially between the ages of forty and fifty. There is achlorhydria, implying loss of the intrinsic gastric factor (pp. 647 and 653), and glossitis, which may be taken as an indication of the probable presence of analogous changes in the mucous membranes of the gastro-intestinal tract, as well as of the pharynx and œsophagus. This type of anæmia may develop after gastrectomy, practically all of the few cases recorded in males coming into this category. Peculiar changes are often found in the finger-nails, *e.g.*, koilonychia [2] or " spoon-nail " and increased brittleness.

The most important factor in the causation of this form of anæmia appears to be a **deficiency of iron,** in addition, in many cases, to repeated pregnancies and lactations, unsuitable diet lacking in fresh vegetables and iron-containing foods such as red meat, and over-indulgence in strong tea, with consequent chronic dyspepsia and achlorhydria (pp. 727–8), any or all of these in individual cases often contributing to aggravate the condition. In connection with the iron-deficiency element in the causation of this variety of anæmia, both insufficient intake in the diet and faulty absorption participate. Menorrhagia is frequently present both as cause and effect; and, since improvement is often rapid after the menopause, endocrine deficiencies and disturbances probably also play a part in its causation.

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[1] We prefer not to use the term " idiopathic " for our main heading as it merely implies that we are still ignorant of the cause.

[2] Koilonychia (κοῖλος, *koilos*, hollow and ὄνυξ, *onux* or *onyx*, a claw or nail), or spoon-nail " is usually associated with anæmia, sometimes, it is said, with gastric ulcer; it is the reverse of the condition of club finger seen in phthisis, etc." Norman Walker and G. H. Percival, " An Introduction to Dermatology," 1939, 10th ed., p. 239.

The **bone-marrow** shows an erythroblastic reaction, but the picture, microscopically, differs entirely from that of Addisonian anæmia, as there is no megaloblastic proliferation. Late macroblasts (late erythroblasts) and normoblasts are present in excessive numbers, but red corpuscles of mature type are so uniformly diminished in size and hæmoglobin-content that the error would seem to be due to the loss of the capacity of the normoblasts to undergo proper maturation into fully-developed red corpuscles.

The **spleen** is enlarged and shows proliferation of the reticulo-endothelial cells without any evidence of fibrosis.

In the **blood,** the red corpuscles are hypochromic and microcytic, and often show only a moderately diminished total count, amounting perhaps to 4,000,000 or more ; but the hæmoglobin is, in a well-established case, generally reduced to 50 per cent. or less, and, as stated above, the colour-index is therefore also low, perhaps only about 0·5 or 0·6 of unity. This lack of hæmoglobin gives the so-called "annular" appearance to the red corpuscles, owing to the increased central pallor resulting from deficiency of hæmoglobin in the central area, and its presence in more normal amount at the periphery. Reticulocytes are scanty in untreated cases, but become much more numerous on the administration of iron. Nucleated red cells are seen only occasionally in the blood-films.

The leucocyte-picture is sometimes unchanged, though there is often a reduction of the total count, generally without much alteration in the differential percentage-figures.

It is in connection with this type of anæmia that **upper dysphagia** or **Paterson's syndrome** [1]—often erroneously called the "Plummer-Vinson syndrome"—(**anæmia** with **atrophic glossitis**—atrophy of the papillæ of the tongue—and **dysphagia**) may occur (p. 705). These symptoms are regarded by some as due entirely to the anæmia (Witts), and by others as caused by degenerative changes in the gangliated nerve-plexus lying between the longitudinal and circular layers of the muscle, corresponding with the plexus myentericus of Auerbach of the intestine (Hurst). Vinson (1922), who first reviewed a considerable number of such cases, considered that the dysphagia was a "hysterical" phenomenon ; but this view is contradicted by the fact that, as pointed out by Paterson (1919), **carcinoma** of the mouth, pharynx and œsophagus, especially at the pharyngo-œsophageal junction, has an abnormally high incidence as a sequel of the chronic and irritative degenerative lesions seen in the subjects of chronic hypochromic anæmia.

3. NUTRITIONAL ANÆMIA of INFANTS

This condition arises in infants at about the age of three months and is due to insufficiency of iron in the diet, usually on account of the substitution of cow's milk for the maternal milk, the latter normally containing a higher iron-content. The importance of the disease lies in an associated increased liability to infection rather than to any definite symptoms arising from the anæmia itself.

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[1] See A. F. Hurst's letter entitled "Paterson's (so-called Plummer-Vinson) Syndrome" in *Brit. Med. Jour.*, 1939, 1, 1201, stating that this disease was first described by the late Dr. D. R. Paterson in 1906, and "should obviously be known as 'Paterson's syndrome' if 'upper dysphagia with anæmia' is regarded as too long a name."

4. ADDISONIAN or "PERNICIOUS" ANÆMIA [1]

Early in last century, two Edinburgh physicians, J. S. Combe and George Kellie, in collaboration, described their clinical and post-mortem observations, made in 1821, on what is probably the first recorded case of "pernicious anæmia," a man forty-seven years of age, who was found dead after the storm of November 3rd, 1821, when he had been on his way on foot from Leith to Musselburgh. Dr. Kellie, in his "Report to the Magistrates" and in his paper read before the Medico-Chirurgical Society of Edinburgh,[2] stated :—

> that he had just had the opportunity of examining, along with his friend Dr. Combe, "the body of a man who exhibited, during life, as perfect an example of anæmia as any perhaps on record. His countenance and his skin every where was of a pale transparent yellow bombycious [3] colour, such as, on first inspection, would naturally suggest the possibility of a liver disease, but then the conjunctiva had nothing of this yellow tinge, neither the urine nor the stools gave evidence of hepatic obstruction . . . the viscera of the thorax and abdomen exhibited no appearance of structural disease. The heart was flaccid and remarkably pale. . . . The body in general was . . . nearly bloodless . . . the medullary part [the white matter] of the brain was uncommonly white and the cineritious part [ash-coloured grey matter] was of the palest grey colour . . . the brain itself soft and watery." For purposes of the comparison of his findings in this patient with those seen in other cases of sudden death, Dr. Kellie then goes on to acknowledge his indebtedness to Dr. Monro, of "interventricular-foramen" fame, then Professor of Anatomy in the University, "who," he says, "very politely afforded me the opportunity of being present at the examination of the bodies of hanged criminals" "whose bodies were commonly sent to him." Professor Monro had informed him that, in his notes on such cases "particular mention is made of the softness of the brains of criminals" (!)
>
> On May 1st, 1822, Dr. Combe himself read a subsequent paper on the same subject before the Society, and called attention to this "very peculiar disease . . . altogether overlooked by any English author with whose writings he was acquainted . . . anæmia as constituting a morbid state *sui generis*," of which this case he is describing "may be considered an example . . . in its most idiopathic form"—a description not unknown even in modern medical literature—and he adds the interesting comment that the patient had "never been blooded." His notes on the post-mortem included the observations that the subcutaneous fat was scanty and pale yellow, the body very bloodless, the heart pale, the liver light brown, and the spleen soft and like a flabby sac, the stomach and intestines though "perfectly sound," were "thin and transparent." With regard to the causation of this "idiopathic anæmia," Combe then made the suggestion that "it is probably owing to some disorder of the digestive and assimilative organs that its characteristic symptoms have their origin," thus anticipating, over a hundred years ago, the modern explanation of the "malady."

Thirty-three years later, in 1855, from the writings of Thomas Addison, of Guy's Hospital, the disorder became recognised as a clinical entity ; but it is only because of the discoveries of the last few years that its nature and causation have been elucidated, and the successful treatment of what had hitherto always been regarded as a progressive, " pernicious " and uniformly fatal disease has been rendered possible.

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[1] We give the above heading to this section as a step towards discarding the now obsolescent term "pernicious," given to the disorder when it was still regarded as a uniformly and necessarily fatal disease.

[2] The title of the paper is of great length, but ends with the main heading : "Some Reflections on the Pathology of the Brain," by George Kellie, 1824, *Transactions of the Medico-Chirurgical Society of Edinburgh*, **1**, 194. Dr. J. S. Combe's paper "History of a Case of Anæmia" was read three months later, and is reported on p. 194 of the same volume.

[3] Bombyx is a silkworm, so "bombycious" is presumably the yellow colour of the raw silk of the cocoon.

It occurs most often during later middle life, and is characterised by a severe degree of macrocytic and hyperchromic anæmia resulting from megaloblastic changes of the bone-marrow, due to the non-maturation of the earlier cells of the erythroblastic series consequent upon the lack or insufficiency of the intrinsic factor of W. B. Castle and his co-workers.[1]

The disease is not infrequently associated with what is known as "**subacute combined degeneration**" of the spinal cord (p. 1157), and the two disorders may be regarded as having ætiological factors in common.

Ætiology. The malady, as just stated, is essentially one of adult life, occurring principally in middle-aged, but also found in elderly, persons, and sometimes not developing till old age. The sexes are practically equally liable to be affected.

The essential cause of the disease is now known to be the absence from the gastric juice of the so-called "**intrinsic factor**" of Castle—a ferment-like substance which, by its action upon an "**extrinsic factor**" contained in the diet, produces a "**hæmopoietic substance,**" now known as **hæmopoietin,** which is capable of being absorbed from the intestine and stored in the liver and kidneys. This " stored substance " is essential for the proper **maturation of the megaloblasts and macroblasts** or **early erythroblasts** of the bone-marrow into normoblasts. Lack of the hæmopoietic substance not only prevents this normal process of maturation, but also leads to a reversion to a primitive megaloblastic state of the bone-marrow whereby very few normoblasts (from which in turn the non-nucleated erythrocytes would normally be formed) are produced, and there is also an escape of varying numbers of **megaloblasts** and **macroblasts** directly into the circulation. Thus there is brought about a gradual reduction in the number of fully-developed circulating erythrocytes.

In Addisonian anæmia, **achlorhydria** (pp. 727–8) has long been known to occur as an almost invariable accompaniment of the disorder—hydrochloric acid is present in perhaps only between 1 to 2 per cent. of cases. It is now known that, following the failure of hydrochloric-acid production, there is, at a later period, failure also to produce pepsin—the condition of **achylia**—and finally a **failure to form the "intrinsic factor"** of Castle. In patients with achlorhydria and achylia, but in whom there is no deficiency of the intrinsic factor, any anæmia which may supervene is *not* of megaloblastic, *i.e.* *not* of " pernicious," type ; and, similarly, in the small minority of Addisonian patients who do *not* suffer from achlorhydria and achylia, the megaloblastic character of their disorder may be traced to the deficiency in the " Castle-factor."

The insidious onset of the disease is explained by the variations in the rate of failure—often very gradual—of the different gastric or gastro-intestinal functions. Thus, in typical cases of Addisonian anæmia, the disorder is due to loss of the intrinsic factor which in turn leads to a failure in the production of the hæmopoietic substance necessary for the proper maturation of the red blood-cells. A certain amount of storage of hæmopoietic substance can be induced by feeding the patient on liver, liver-extracts, kidney or brain from animals, for all these contain the hæmopoietic substance in varying amount. Alternatively, by administering desiccated preparations of hog's stomach, some of the hæmopoietic substance, together with both intrinsic and extrinsic factors, are provided, and a further supply of the hæmopoietic substance may then be formed.

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[1] *Amer. Jour. Med. Sci.*, 1930, **179**, 305.

In connection with the problems both of normal and of abnormal erythropoiesis, the work of W. Jacobson [1] (1939) upon **argentaffine** (or **argyrophil**) **cells** (discovered by R. Heidenhain in 1870) is important. The former has investigated the **distribution** of the argentaffine cells of the gastro-intestinal tract corresponding with the areas from which the "**intrinsic factor**" of Castle can be extracted, and the investigations of Jacobson and others make it appear probable that these cells are concerned in its production. The areas involved are the cardiac and pyloric regions (but *not* the fundus) of the stomach : the duodenum and, in decreasing degree on passing downwards, the rest of the small intestine and colon. These argentaffine cells possess **cytoplasmic granules** with a yellowish coloration of their own, visible in unstained microscopical preparations. They are also chromaffine (to bichromate) and form a diazo-dye with diazo-compounds in alkaline solution : but the most reliable means of demonstrating their presence is Masson's method of the reduction of ammoniacal silver nitrate whereby they are impregnated and blackened. They are fluorescent and also give positive micro-chemical reactions for pyramidine and purine-derivatives (*e.g.*, by the murexide test) : and for a carbohydrate, probably pentose ; and it may be noted that a similar and probably identical purine has been isolated from active liver-extracts, successfully used for the treatment of Addisonian anæmia.

Jacobson, in his learned and interesting paper, explains that the yellow-coloured substance in these granules is "xanthopterine," one of seven known "pterines," which are so called because they give the colours to the wings of butterflies. The interest of these argentaffine cells to us here is that they are believed to have either a secretory or an endocrine function associated with production of the intrinsic hæmopoietic factor. The cells are found to be much reduced in number or absent in Addisonian anæmia, and also in the tropical macrocytic anæmia associated with sprue ; but they are not entirely absent in certain atypical macrocytic anæmias which are refractory to liver-treatment. They are not appreciably reduced in non-macrocytic anæmias. Histological material suitable for their demonstration must be fresh and collected and fixed not more than six hours, preferably less, after death. Certain tumours of the intestine originate in, and are largely composed of, these argentaffine cells (pp. 756–7).

It must be remembered, however, that, apart from the possible absence of the necessary hæmopoietic substance, a failure of absorption of this substance even when present would equally well lead to the establishment of the Addisonian state, as would also any cause leading to a destruction of the substance after it had been formed. *Diphyllobothrium* infestation appears to provide the latter type of condition (*cf.* p. 665). In gastric carcinoma or in cases of extensive surgical interference with the stomach, the intrinsic factor is often absent, perhaps because of the destruction or removal of the argentaffine cells. In tropical macrocytic anæmia, the failure of maturation may be due to similar causes, as well as to lack of the extrinsic factor in the diet, whilst, in widespread disease of the liver, there is a possibility of failure on the part of that organ to store the hæmopoietic substance, even though the formation of the latter and its absorption have both occurred normally.

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[1] W. Jacobson, Strangeways Research Laboratory, Cambridge, "The Argentaffine Cells and Pernicious Anæmia," *Jour. Path. and Bact.*, 1939, **49**, 1–19. In this paper Jacobson gives full references to the literature of the subject. In this connection see also our chapter on Diseases of the Digestive System, pp. 727–8.

It is due largely to the multiplicity of the factors capable of causing or leading to a failure in any part of the chain of events constituting normal erythropoiesis, that hitherto the grouping together of various disorders as "pernicious" has, on detailed examination, proved not to be fully justified.

Changes in the Blood. These vary with the stage of the disease, especially in regard to the remissions which are often a feature in some cases of Addisonian anæmia : and also at the present day with any inadequacy of treatment. In untreated cases or during a relapse when treatment has been insufficient or neglected, the blood is of thin consistency with a tendency to the separation of its formed elements, so that a "streakiness" is apparent when the droplets of blood are collected for examination. The plasma contains an excess of bilirubin, producing the characteristic lemon-yellow staining of the skin, fat, and other tissues ; and, in the fæces and urine, there is greatly increased excretion of porphyrin.[1] The total bulk of the blood is reduced ; and its coagulability is diminished.

In untreated cases, the red corpuscles show a great and progressive diminution in numbers, for example, to about 1,000,000 ; and, in advanced cases, the count may lie between 600,000 and 300,000 per c.mm. In shed blood, the corpuscles lose their natural tendency to form rouleaux. **Poikilocytosis** (Plate XVIII, opposite p. 650, Fig. 1 : and *cf.* Fig. 4) is a constant feature, as are also great alterations in the **size** of the corpuscles, this **variability** being almost as significant as the characteristic **macrocytic** element in the anisocytosis. In a series of cases collected by Price-Jones [2] (1929), the mean diameter of the red corpuscles in Addisonian anæmia varied from 7·5 to 9·5 μ, with an average of 8·3 μ, as compared with the normal average of 7·2 μ in healthy individuals. In obtaining these figures Price-Jones used dried stained films. Other observers measure the red corpuscles fresh and in their normal environment, *i.e.*, whilst still immersed in their own plasma, the results being then slightly greater, the normal mean diameter being 7·6 μ in place of the 7·2 μ in dried films. For ordinary clinical purposes we ourselves usually take 7·5 μ as a convenient and sufficiently accurate normal figure, with variations of, say, 0·5 μ above and below it, *i.e.*, 7 to 8 μ. In Addisonian anæmia, unusually small forms or microcytes are often present, but the abnormal cells most characteristic of this form of anæmia are **megalocytes** and **hæmoglobinised megaloblasts** and **macroblasts,** especially the two last, which, after early infancy, are not found in any appreciable numbers in the blood except in this disorder, and may measure 10, 12, and perhaps 15 μ or more in diameter. Certain of these non-nucleated and nucleated red corpuscles are of such large size—*e.g.*, exceeding even 20 μ in diameter—that the terms gigantocyte and gigantoblast have been applied to them. Normoblasts may also be found, but are seldom numerous except in advanced stages of the disease. The numbers of nucleated red cells in the blood may, in some patients, increase remarkably after transfusion. Megaloblasts, macroblasts and normoblasts often exhibit karyorrhexis or nuclear fragmentation, and, very occasionally, true mitosis may be observed in them. The various forms of red corpuscle frequently show other degenerative changes, *e.g.*, polychromatophilia, punctate basiphilia and granular degeneration, as well as the poikilocytosis already mentioned (Plate XVIII, opposite this page, Fig. 1). Nuclear remains (Cabot rings—Howell-Jolly bodies) are sometimes present within them. Although the total amount of hæmoglobin present in the blood may fall to 30 per cent. or less of the normal, yet, in relative proportion to the number of red corpuscles present, it may not only not be diminished, but the amount per corpuscle may even be increased. The **colour-index** or hæmoglobin-index is almost invariably above unity, often 1·2, and may reach 1·6, a phenomenon due in part to the larger size of many of the red corpuscles. Whether there is any actual condensation of their contained hæmoglobin in some of the corpuscles which stain more deeply than the others is still a debated question—the chemical composition of the hæmoglobin itself, however, probably remains constant.

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[1] In this instance, the isomer "coproporphyrin I" : *see* "Hæmoglobin Metabolism," by M. C. G. Israëls, *Lancet*, 1941, ii, 443.

[2] *Price-Jones Curve.* Full details of his methods of measuring red corpuscles in stained films, the plotting of the curves so obtained, and their interpretation, are given by C. Price-Jones in his paper : "Red Cell Diameters in One Hundred Healthy Persons and in Pernicious Anæmia : The Effect of Liver Treatment," *Jour. Path. and Bact.*, 1929, **32**, 479, and may also be found in special textbooks of Hæmatology. For the convenience of our readers, we append his own "Summary" of his paper, pp. 492–3 :—

"1. The average mean diameter of red blood corpuscles determined by measuring 500 cells in each of 100 healthy adults by the dry film method is 7·202 μ : the healthy range is from 6·686 μ to 7·718 μ.

"2. The healthy range of the coefficients of variation is from 5·33 to 7·32 with a mean of 6·33.

"3. An excessive variability is even more constant in pernicious anæmia than a high mean diameter.

"4. Methods of measuring the degree of megalocytosis are discussed and defined.

"5. The effect of treatment must be gauged in the light of the range of healthy variation.

"6. Liver treatment, effective in curing the anæmia, brings the red cell diameters and variabilities towards or within the healthy range but a completely normal position is reached only in a proportion of cases."

The leucocytes are, as a rule, reduced, usually to about half their normal numbers, the diminution affecting especially the **polymorphs,** owing to the hæmopoietic energies of the marrow being directed towards the production of cells of the erythroblastic series. Even intercurrent infections may fail to stimulate the production of a leucocytosis in these cases. It is not uncommon to find occasional, and sometimes many, polymorphs of larger size than normal, and, on the analogy of the terminology used for the abnormal red corpuscles, these are sometimes called " macropolymorphs " or " macropolycytes." It is noticeable that the nuclei of these, and sometimes of the polymorphs of ordinary size, are exaggeratedly " polymorphonuclear " in character, *i.e.*, have many more lobes than usual, and occasionally even come to resemble small megakaryocytes with " basket-shaped " nuclei. The lymphocytes may be relatively less diminished in numbers than the polymorphs. The number of blood-platelets is usually much decreased, but they may show undue irregularity or inequality in size.

DESCRIPTION OF PLATE XVIII

PLATE XVIII

FIG. 1. *Blood-Film from a case of Addisonian Anæmia* (stained with eosin and methylene-blue). × 500

a. Polymorphonuclear leucocyte.
b.b. Normocytes.
c.c. Various erythrocytes showing polychromatophilia, or diffuse basiphilia.
d. Normocyte showing punctate basiphilia.
e. Normoblast.
f. Normoblast showing karyorrhexis *f′*, *f′*. Nucleated red corpuscles, more or less intermediate between normo- and macro-blasts, also showing karyorrhexis.
g. Normoblast showing punctate basiphilia.
h. Megalocyte.
i. Macroblast.
k. Macroblast showing punctate basiphilia.
l.l. Microcytes (some probably formed by fragmentation of larger cells).
m.m. Poikilocytes.

FIG. 2. *Blood-Film from a case of Chlorosis* (stained by Leishman's Method—note that, in the reproduction, the staining has come out rather too dark, the pale centres of the erythrocytes not being well shown). × 500

a. Polymorphonuclear leucocyte.
b. Medium-sized lymphocyte.
c. Normoblast.
d. Blood-platelets.

FIG. 3. *Bone-Marrow Film* (*Rib*) *from a case of Pneumococcal Empyema, showing Leucoblastic Reaction* (stained with eosin and methylene-blue). × 500

a.a. Mature polymorphonuclear neutrophil leucocytes.
b.b. Immature polymorphonuclear neutrophil leucocytes.
c.c. Intermediate neutrophil myelocytes or metamyelocytes.
d.d. Neutrophil myelocytes.
d′.d″.d‴. Neutrophil myelocytes showing stages of karyokinesis.
e.e. Non-granular cells, possibly myeloblasts or promyelocytes, *i.e.*, parent-cells of the granular myelocytes.
f. Coarsely granular polymorphonuclear eosinophil leucocyte.
g.g. Coarsely granular eosinophil myelocytes.
h.h. Small lymphocyte-like cells.
i.i. Normoblasts.

FIG. 4. *Bone-Marrow Film* (*Femur*) *from a case of Addisonion Anæmia, showing an Erythroblastic Reaction of Macroblastic type* (stained with eosin and methylene-blue). × 500

a.a. Neutrophil myelocytes.
b. Coarsely granular polymorphonuclear eosinophil leucocyte.
c.c. Coarsely granular eosinophil myelocytes.
d.d. Normocytes.
e.e. Normoblasts showing karyolysis, karyorrhexis, poikilocytosis, etc.
f.f. Macroblasts and megaloblasts showing similar changes (note that all transitions are found between normoblasts, macroblasts and megaloblasts ; hence there is often difficulty in classifying individual cells).
g. Megaloblast with " primitive " type of nucleus.

PLATE XVIII, p. 650.

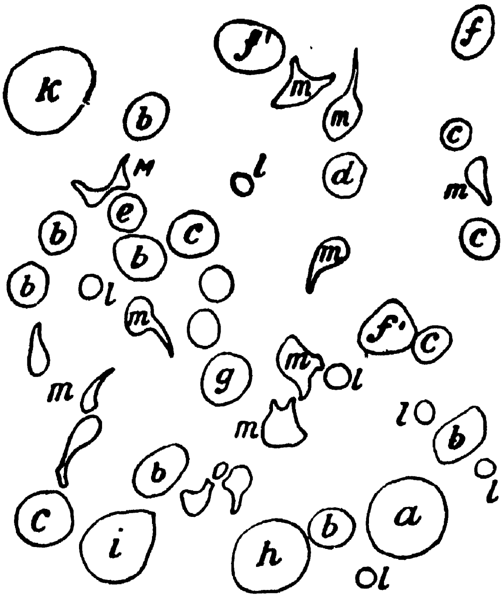

FIG. 1.

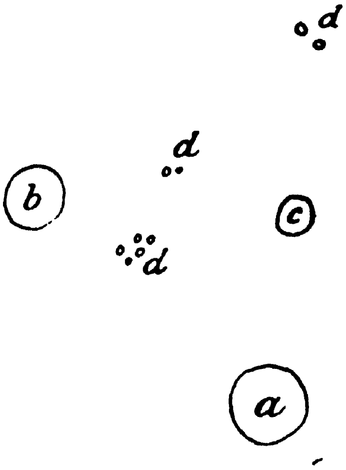

FIG. 2.

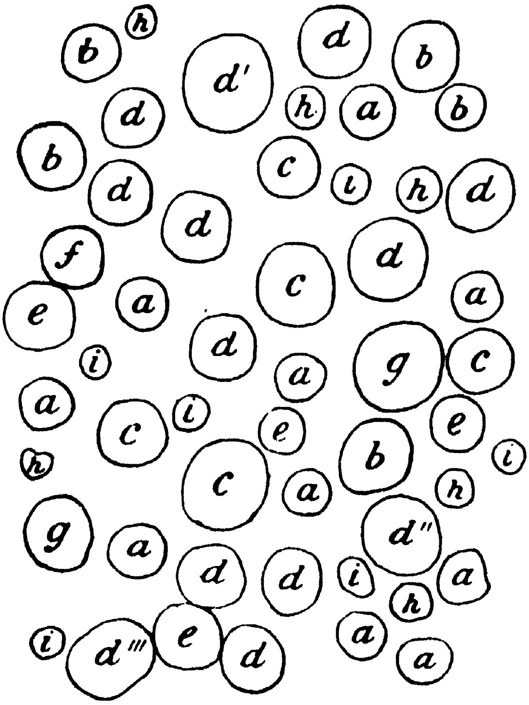

FIG. 3.

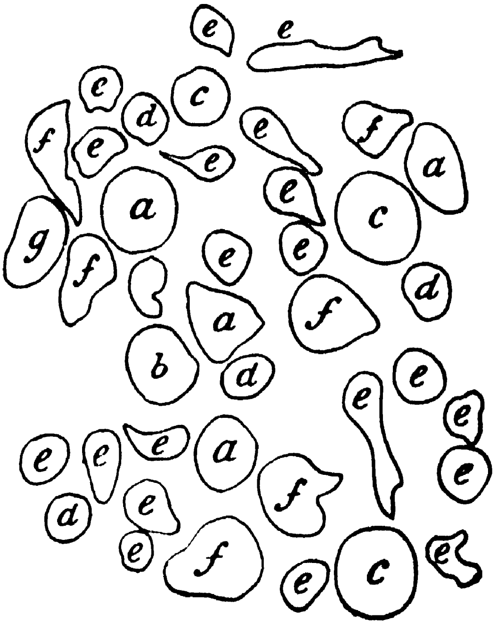

FIG. 4.

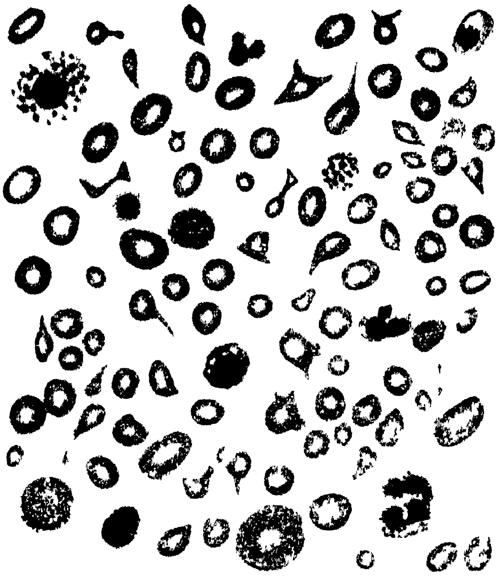

FIG. 1 × 500

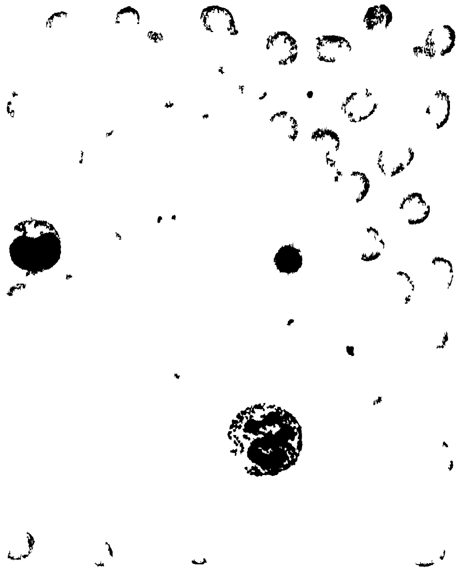

FIG. 2 × 500

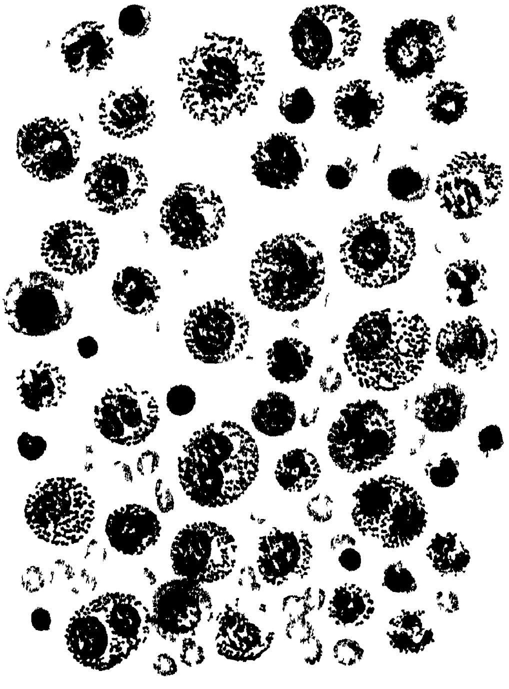

FIG. 3. × 500

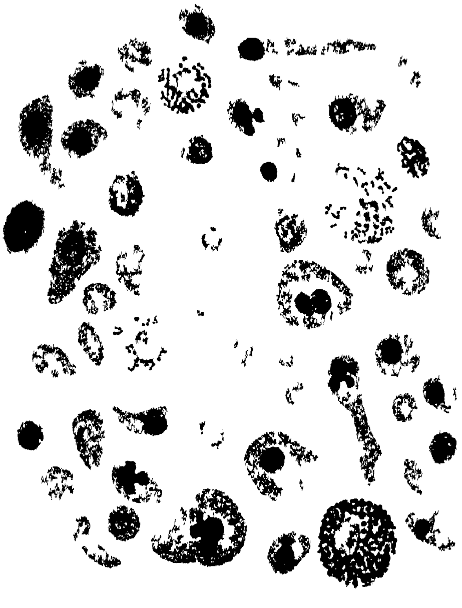

FIG. 4 × 500

The blood-picture is modified profoundly as a result of adequate treatment with the necessary specifics (intrinsic factor, etc.), and in the less advanced cases a return of the blood-picture almost to normal is the rule. A reticulocyte-response is the earliest evidence of successful treatment. On the oral administration of active liver- or hog's-stomach preparations, this shows itself as a definite sudden rise in numbers, beginning on the fourth or fifth day of treatment and the increase lasting some two weeks, with a maximum at the end of the first week of treatment. The response is more rapid on intramuscular, and still more so on intravenous, injection of the extracts. The number of reticulocytes may rise from the normal of 0·2 or 0·4 per cent. up to 30, 40 or 50 per cent. or even more of the circulating red corpuscles (Plate XIV, opposite p. 594).

Afterwards, the red-count rises and the colour-index falls, whilst degenerated and nucleated forms are now no longer to be found in the circulation.

It is usual for the leucocyte-picture also to return approximately to the normal, although sometimes it continues to show a slight degree of leucopenia. Occasionally, however, the polymorph-count is raised to a figure above the normal. The eosinophils [1] are also not uncommonly increased in numbers, especially when raw liver has been the therapeutic agent employed.

Changes in Other Organs and Tissues :—

Bone-Marrow.[2] The changes which occur in this tissue in uncontrolled Addisonian anæmia are characteristic and take the form mainly of an erythroblastic reaction, **megaloblastic** in type (Plate XVIII, opposite, Fig. 4). On sternal puncture, in advanced untreated or imperfectly treated cases, megaloblasts constitute the majority of the total cells present, and are usually far in excess of what might be expected from the examination of the blood.

Myelocytes and other cells of the leucocyte-forming series are diminished in numbers, although the capacity for leucoblastic transformation is often retained, and may show itself in cases where pneumonia or some such leucocytosis-producing complication supervenes.

Another phenomenon, of constant occurrence in the marrow in this disorder when untreated is the presence of large numbers of actively phagocytic cells engaged in the process of blood-destruction or hæmolysis (Plate XI, opposite p. 222, Fig. 2 : Plate XIII, opposite p. 380, Fig. 4 : and Plate XVII, opposite p. 616, Fig. 6). These cells, which are readily demonstrable in fresh-wet or wet-fixed films, but may be comparatively inconspicuous in sections of paraffin-embedded tissues, may contain enormous numbers of red corpuscles, both nucleated and non-nucleated (Plate XVII, opposite p. 616, Fig. 6); or, in other instances, they may be filled with blood-pigment derived from these. The red corpuscles are not only hastily and imperfectly formed in excess, but are also destroyed in excess. These hæmolytic processes in the marrow, if its amount and extent throughout the body be taken into account, form an important function of this tissue only now beginning to be recognised. The fatty tissue disappears, and the medullary cavities of the bones become enlarged by the absorption of the spongy, and even of much of the compact, bone. The marrow is much redder in colour, and its appearance has suggested the comparison to red-currant jelly or raspberry jam. Where much blood-pigment is present, the marrow may be brick-red in colour; or, where a leucoblastic reaction for the production of a leucocytosis is superadded because of the presence of some complication such as pneumonia, it may be of a pinkish or pale-red tint.

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[1] Of a series of cases of Addisonian anæmia, commencing in 1927, in which the writer of this chapter (W. E. C. D.), along with Dr. Worster-Drought and others, observed the occurrence of eosinophilia as a direct result of liver-treatment, the first was a female patient, then aged fifty-five years, whose blood during 1926 and 1927 had shown an erythrocyte-count of 2½ to 3 million and leucocytes averaging just over 7,000 per c.mm., the eosinophils numbering from 2 to 3·5 per cent. With the administration of liver from November, 1927, onwards, the eosinophils suddenly increased to 16·5 per cent. of a total leucocyte-count of between 5,000 and 6,000 per c.mm., and were still 9·6 per cent. in May, 1928. Thereafter they steadily decreased, and on several occasions from 1932 to 1937 eosinophils were even entirely absent from the peripheral blood, and since then they have been present only in small numbers—0·5 and 0·25 per cent. This patient is still (1942) in good health. We found such eosinophilia, though by no means a constant result of liver-treatment, fairly common ; and we have observed it to occur, not only on giving raw liver by the mouth, but also on the administration of various commercial extracts.

[2] These descriptions of the bone-marrow and other organs and tissues are founded mainly upon our observations of post-mortem material obtained previous to the introduction of liver-treatment. There is now, in modern hospital-practice, seldom much opportunity to observe the changes characteristic of untreated " pernicious anæmia."

Liver. The organ may be normal in size or slightly enlarged, the individual lobules being often increased in dimensions, and exhibiting distinct outlines. It has a pale snuff-brownish-yellow or *café-au-lait* tint, due to the combined presence of pigmentation and fatty degeneration. The Prussian-blue reaction with potassium ferrocyanide and hydrochloric acid is used to demonstrate the presence of the hæmosiderin, the iron-containing pigment derived from the hæmoglobin of the destroyed blood-corpuscles (Plate XI, opposite p. 222, Fig. 3). This is present in the form of small granules in, and to a less extent between, the liver-cells, especially at the peripheral parts of the lobules next the portal tracts, where it forms a darker zone which maps out the lobules distinctly.

Spleen (p. 699). This organ may be slightly enlarged in some cases. It has usually, a dark brownish-red colour, and may not give the typical Prussian-blue reaction, the reagents often producing a variable greenish- or bluish-black discoloration. On microscopical examination (especially of wet-fixed film preparations), great increase of hæmolytic activity resembling that seen in the bone-marrow, is demonstrated by the presence of active phagocytosis, especially on the part of the endothelial cells of the pulp, these cells often attaining a large size and containing numbers of ingested red corpuscles and pigment-granules.[1]

Kidneys. The kidneys are usually of a pale brownish-yellow tint, from the presence of hæmosiderin-pigment, combined with intense fatty degeneration in the cells of the convoluted tubules and ascending parts of Henle's loops.

Heart and Vessels. The heart generally shows profound fatty degeneration, usually most advanced in the inner part of the muscle of the left ventricle. This fatty change is often distinctly patchy in its distribution, and may show through the endocardium as irregular yellowish-white spots or patches, usually best seen on the papillary muscles and interventricular septum—the so-called "thrush-breast" or "tabby-cat" appearance (p. 200).

The endothelium of the **smaller vessels** and **capillaries,** *e.g.*, in the pia, omentum, etc., may show widespread fatty degeneration; and hæmorrhages may be found, *e.g.*, in the retina, subcutaneous tissues, serous and mucous membranes and central nervous system. **The lungs** commonly show a condition of atrophous or " small-lunged " emphysema, and perhaps a terminal œdema.

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[1] *See* Plate XIII, opposite p. 380, Fig. 4: and Plate XVII, opposite p. 616, Fig. 6. The phagocytic cells in wet-fixed films of the spleen-pulp are practically identical with the reticulo-endothelial and other phagocytic cells of the bone-marrow shown in these illustrations.

In the central nervous system, especially in the spinal cord, certain degenerative lesions are a not unusual accompaniment of Addisonian or " pernicious " anæmia, especially in the dorsal, or dorsal and lateral, columns (*see under* Subacute Combined Degeneration, p. 1157 *et seq.*).

Gastro-intestinal Tract. The changes in this, both clinical and pathological, are important and significant. The condition of the **tongue** is almost always of diagnostic value, and " sore tongue " or " sore mouth " is not infrequently the first complaint which brings a patient with Addisonian anæmia to his doctor. The tongue may at first be smooth and glazed, but tends later to become bright red, raw and " beefy," and perhaps cracked and ulcerated, sometimes severely—a combination of malnutrition and inflammation usually described as a "**glossitis**" (p. 705), attention to which was first called by William Hunter.[1] Manson-Bahr [2] emphasises the occurrence of this characteristic glossitis in a number of allied conditions (see below, p. 654, and also p. 705) and believes that vitamin-B_2 deficiency may at all events partially account for this and many of the other lesions common to pellagra, tropical and non-tropical sprue, " idiopathic " steatorrhœa and nutritional megalocytic anæmia (due to absence of the extrinsic factor), as well as of Addisonian anæmia. A sufficiency of vitamin C (p. 443) is also essential in the treatment of Addisonian and other forms of anæmia.

As noted by Drs. Kellie and Combe over a century ago (p. 646), the walls of the **stomach** and **intestines** tend to become " thin and transparent " ; and the almost constant association of **achlorhydria** and **achylia** (diagnosed during life by the examination of a fractional test-meal) is of great significance, as is also the deficient production of the gastric "**intrinsic factor,**" the last perhaps to be explained by the diminution or absence of the **argentaffine** (or **argyrophil**) **cells** in the gastro-intestinal tract (p. 648).

We have mentioned elsewhere the importance of the hydrochloric acid as an " antiseptic " agent in the stomach and intestine, and its absence allows of the growth of various harmful bacteria such as streptococci and *Cl. welchii.* Some of the ill-effects of such interference with gastric function are found also in cases of **carcinoma of the stomach,** and, when there is interference with the production of the " intrinsic gastric factor " it is understandable that the resulting anæmia may occasionally take on macrocytic or " pernicious " characters.

Achrestic Anæmia.[3] Certain rare cases closely resemble Addisonian or " pernicious " anæmia, in that they are **hyperchromic** and **macrocytic,** but on the other hand *do* show the presence of **free hydrochloric acid** in the gastric secretion, and moreover fail, partially or completely, to respond to treatment with active liver-preparations. In these patients the liver itself seems already to contain the anti-anæmic principle, and the disease is therefore not due to its absence, but, it is believed, to the inability of the patient to utilise or to mobilise it although present—hence the term " achrestic " applied to this form of macrocytic anæmia.

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[1] *The Severest Anæmias,* London, 1909.

[2] *See* footnote on p. 654.

[3] From Greek ἄ-χρηστος, *a-chrēstos,* unable to make use of, from ἀ-privative and χράομαι, *chraomai,* I use or utilise.

5. ANÆMIA OF SPRUE

Sprue is a tropical disease characterised by chronic diarrhœa leading to severe wasting and anæmia which, in its earlier stages, is of hypochromic and microcytic type, but in the later stages tends to become macrocytic and hyperchromic and practically identical in its blood-picture with that of Addisonian anæmia. These changes in the hæmatological picture are accounted for by variations in the factors which are at work inducing the anæmia. At one period there may be lack of the intrinsic factor, at others failure to absorb this substance, whilst in other cases again the diarrhœa itself leads to the production of a simple type of anæmia associated chiefly with lack of iron-absorption.

Atrophic glossitis, similar in its characters to that of Addisonian anæmia, is found also in sprue, as well as in pellagra, the nutritional anæmias and idiopathic steatorrhœa or non-tropical sprue. Subacute combined degeneration of the spinal cord (p. 1157) also occurs in sprue, but only very occasionally, and Manson-Bahr suggests that a deficiency of the vitamin-B_2 complex, which appears to be common to all of these disorders, may partially explain such phenomena, borderline-cases between them being often encountered.[1] The internal organs all show evidence of atrophy, as a result of general malnutrition, and this is especially prominent in the bowel, which may show extreme thinning of the wall due to atrophy of the muscular coats and hypoplasia of the mucosa.

6. THE ANÆMIAS OF PREGNANCY

Anæmias of several types may be found associated with pregnancy, for not only may the pregnant woman develop an anæmia during her pregnancy, and often as a result of it, but the pregnancy may itself have supervened in a case of already established anæmia. Thus, inclusion of it here among the series of anæmias of nutritional origin is justified only in so far as the commonest variety arising during pregnancy is concerned, namely a hypochromic anæmia associated with iron-deficiency (p. 644). Other types of anæmia associated with pregnancy receive mention in the next section, which deals with anæmias resulting from toxic factors (p. 655), and still further varieties are described in the section on "hæmolytic" types of anæmia (p. 658). A severe type of anæmia associated with a megaloblastic condition of the bone-marrow and simulating or resembling Addisonian anæmia sometimes occurs during pregnancy or the puerperium, but from which there may be complete recovery under appropriate treatment by blood-transfusion, etc.

The hypochromic anæmia of pregnancy is in some instances merely an exaggeration of a pre-existing and milder degree of hypochromic anæmia. More frequently, however, the condition arises directly as a result of the pregnancy itself, and is then due to factors such as lack of iron in the diet owing perhaps to capricious distaste for iron-containing foods.

The red-count falls, perhaps, to 3,500,000, with a hæmoglobin-content of 50 per cent. or less. Nucleated red cells are often numerous, and corpuscles showing polychromasia also occur. Treatment with iron will produce a definite reticulocyte-response, followed, in most cases, by improvement in the red-count.

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[1] "Glossitis and Vitamin-B_2 Complex in Pellagra, Sprue, and Allied States," by P. Manson-Bahr, *Lancet*, 1940, ii, 356.

(b) GROUP OF ANÆMIAS DUE TO THE ACTION OF CHEMICAL AND PHYSICAL AGENTS

The anæmias here considered tend to overlap the group described later as the " hæmolytic anæmias " (pp. 660 and 664), but for the sake of systematic description some mention of them is necessary here also.

Anæmia produced by the action of the X-rays or of radium on blood-forming tissues was recognised first among the early X-ray workers in whom a severe anæmia of aplastic type occurred, and the therapeutic action of irradiation of the bones and spleen has been utilised in cases of over-production. More recently, analogous conditions have been found among factory-operatives as the result of handling radio-active material for various commercial purposes, such as painting the " luminous " dials of watches..

The anæmia which develops under trade-conditions is of hyperchromic and macrocytic type and appears to result from the action of Alpha-rays. Anisocytosis is usually a marked feature, with the presence of few nucleated cells, some of macroblastic or of megaloblastic type.

Workers in the radiological departments of medical practice are also exposed to Gamma-rays originating from an external source instead of within the body as in the case of the factory workers, by whom the radio-active material is for the most part swallowed in minute quantities. The anæmia resulting from this **external** action tends to be aplastic, but the process is slow, and in the early stages is associated with anisocytosis and a tendency towards increased size of corpuscles and changes in the leucocytes which, though inconstant, take the form of a decreased count, accompanied sometimes by increase, absolute or relative, of eosinophils and monocytes.

In **sepsis** and some types of **poisoning**—particularly with the metallic poisons—and, as already indicated, the strain and sometimes the perverted metabolism of **pregnancy**—the anæmia which results can be ascribed to a toxic influence affecting the nutrition and activities of the hæmopoietic system.

The prolonged or excessive absorption of mercury or arsenic and also of lead, whether for therapeutic or cosmetic purposes or from trade-exposure to them, the first action of which, in sufficiently small amount, is stimulating to the hæmopoietic system, is followed later by an aplastic anæmia of this nature. The punctate basiphilia which is characteristic of chronic lead-poisoning is observed, not only in the erythrocytes, but also in the erythroblasts.

(See also under Groups III and IV on pp. 663 and 664 for Anæmias due to other known causes.)

II. THE HÆMOLYTIC ANÆMIAS

In this rather indefinite group of " **hæmolytic** " disorders, **destruction of the red corpuscles takes place *within* the vascular system** itself, as contrasted with disorders in which there is, on the one hand, **defective production of erythrocytes in the bone-marrow**: or, on the other, actual **extravascular loss of blood by hæmorrhage,** either external to or into the body-tissues or cavities (p. 663). It is often difficult to determine whether the destruction of erythrocytes in the circulating blood within the vessels is due to increased fragility of the corpuscles themselves or to their excessive destruction by toxic or other agents : or in some instances to **both** of these factors. Such increased hæmolysis, *i.e.*, actual blood-destruction, is characterised by an increase of the icteric index of the blood-serum, a positive van den Bergh reaction (p. 229), and, usually, some degree of jaundice clinically, together with an excess of urobilinogen (and urobilin) and porphyrin (" coproporphyrin ") in the urine and fæces, and, in the more acute and severe cases, by varying degrees of hæmoglobinuria. As is so often the case in other pathological conditions, without full knowledge and understanding of their causes, classification is still unsatisfactory, and in this the hæmolytic anæmias are no exception ; and, where we are still uncertain of their direct cause, we are even yet apt to label them " primary " or " idiopathic "—terms which in the past have been applied, for example, to Addisonian or so-called " pernicious " anæmia.

HÆMOLYTIC ANÆMIA WITH ACHOLURIC JAUNDICE

Though a comparatively rare disorder, this syndrome has attracted much attention because of the peculiar **alterations in the shape and size** of the red corpuscles in the circulating blood and their **increased fragility**—phenomena involving problems of considerable scientific interest and importance.

The numerous synonyms employed to designate the disease serve to indicate the varied views as to its nature emphasised by different writers—for example, " **acholuric family jaundice,**" " **congenital hæmolytic anæmia,**" " **hæmolytic icterus** " and " **chronic splenomegalic hæmolytic jaundice.**"

Two main varieties of the malady are recognised by clinicians, the " **congenital** " and the " **acquired,**" but there is still a certain amount of doubt as to whether some, at all events, of the rare examples of the latter hitherto recorded may not have been due merely to some secondary or exciting causal factor precipitating an attack in a patient in whom the congenital disorder is already present in latent form.

In its " **congenital** " form, the disease is transmitted by either of the parents to male and female offspring alike, *i.e.*, as a Mendelian dominant. It is thus apparently a heredo-familial disorder attacking siblings of the **same** and relatives of **several** generations,[1] and is believed by many to be due to an " inborn abnormality " whereby the bone-marrow produces unduly spherical erythrocytes, biconvex instead of biconcave, and of smaller diameter than normal—between 6 μ and 7 μ—in place of the normal between 7 μ and 8 μ—and sometimes described as **micro-spherocytes,** though the actual volume remains practically the same (Fig. 358, p. 586). Recent experimental work by

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[1] In the *Lancet* of July 20th, 1940, p. 83, there is an interesting letter headed " Daffodil and Orange," from Dr. F. J. Poynton, late of the Hospital for Sick Children, Great Ormond Street, now of Bath, in which he tells of a father who, about the year 1903, along with his three daughters, was shown at a meeting of the Association of Physicians in London, as examples of the then newly recognised condition of familial or acholuric jaundice. The father was orange-coloured, the daughters daffodil. " Later, as knowledge increased, his spleen was removed," and he is now (in 1940) " 72 years of age, in fine health and able to read without glasses." In the same issue of the *Lancet*, p. 73, there is an editorial article on " Hæmolytic Jaundice," giving a summary of the experimental work of Dameshek, Schwartz and Gross to which we refer here.

Dameshek, Schwartz and Gross,[1] however, suggests that these abnormalities—at all events in the series of cases investigated by them—are, or may be, brought about by the action upon the corpuscles themselves of **hæmolysins** circulating in the blood, and these writers believe that the exaggeratedly erythroblastic character of the bone-marrow is due rather to the effort of the tissue to **replace** the abnormally spherical, and therefore, they believe, unduly fragile, corpuscles destroyed by the actively phagocytic cells of the reticulo-endothelial system throughout the body, but especially that of the enlarged spleen. They claim to have demonstrated in the blood of three of their four patients the existence of these hæmolysins which are of the nature of immune-bodies (p. 129, *et seq.*) similar to those of the hæmolytic system used as indicator in the Wassermann and other complement-fixation reactions. These hæmolysins they find to be not only **auto-hæmolytic,** *i.e.*, destructive of patients' *own* corpuscles, but also **iso-hæmolytic,** *i.e.*, will hæmolyse the corpuscles of persons *of the same blood-group* as the patient, as well as those of Group *0* (Moss Group IV) (p. 589). From the examination of biopsy-specimens of bone-marrow obtained by sternal puncture, they claim to have found, as noted above, that the reaction in the marrow is normoblastic, not "microspherocytic," and that it is merely of the nature of an increased production by the marrow of ordinary red corpuscles to replace those damaged and rendered globular by the injurious action of the hæmolysins, and then, because of their *subsequent* change in shape and increased fragility (*cf.* Fig. 357, p. 586), destroyed in excessive numbers by the over-active spleen.

By the **experimental injection** of suitably graduated doses of **hæmolytic immune-body** (rabbit's serum *versus* guineapig's corpuscles), Dameshek and Schwartz were able, in the latter animal, to reproduce blood-pictures corresponding to those of the various grades of hæmolytic anæmia occurring "naturally" or "spontaneously" in the human subject,[2] and, from their

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[1] "Hemolysins as the Cause of Clinical and Experimental Hemolytic Anemias: with Particular Reference to the Nature of Spherocytosis and Increased Fragility," by William Dameshek, Steven O. Schwartz and Sonya Gross, Boston, Mass., *Amer. Jour. Med. Sciences*, 1938, **196,** 769–792: and "Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type)," by W. Dameshek and S. O. Schwartz, *Medicine*, 1940, **19,** 231–327. The latter article gives an excellent account of the varieties of hæmolytic anæmia, with full references to the literature.

[2] **Hæmolytic Syndromes :—**

EXPERIMENTAL :	CLINICAL.
Large dosage. Fulminating hæmolytic anæmia with hæmoglobinuria.	Acute paroxysmal hæmoglobinuria : Fulminating acute hæmolytic anæmia with hæmoglobinuria. Hæmoglobinuria with hæmolytic anæmia.
Medium dosage. Acute hæmolytic anæmia : (*a*) With spherocytes predominating. (*b*) With reticulocytes predominating.	Acute hæmolytic anæmia ("Febrile," "Lederer's") : (*a*) With spherocytes predominating. (*b*) With reticulocytes predominating. "Crisis" of chronic hæmolytic anæmia : (?) Erythroblastosis fœtalis.
Small dosage. Subacute hæmolytic anæmia with pseudo-macrocytic blood-picture. **Continued small dosage** (?). Chronic hæmolytic anæmia (not yet produced).	Subacute hæmolytic anæmia with "pseudo-macrocytic" blood-picture (often mistaken for Addisonian or "pernicious" anæmia). Chronic hæmolytic anæmia with spherocytic blood-picture (congenital).

clinical and experimental studies, these authors propose the following classification of clinical types of hæmolytic anæmia :—

(A) **Congenital Hæmolytic Anæmia (Icterus).**[1]
- 1. **Chronic,** with or without crisis.
- 2. **Subacute.**
- 3. **Acute** (crisis).

(B) **Acquired Hæmolytic Anæmia (Icterus).**[1]
- 1. **Secondary** to known causes (infective, chemical, " toxic," pregnancy, etc.).
- 2. **Symptomatic,** in association with certain grave, and usually fatal, diseases, such as lymphatic leukæmia, lymphadenoma and carcinomatosis.
- 3. **Of unknown causation,** with or without **hæmolysins** in the plasma.
  - (*a*) **Chronic,** with or without crisis.
  - (*b*) **Subacute.**
  - (*c*) **Acute.**
  - (*d*) **Acute fulminating,** often with **hæmoglobinuria.**

(A) **CONGENITAL HÆMOLYTIC ANÆMIA (Congenital Hæmolytic Icterus or Acholuric Jaundice).** Enough has already been said to explain the views of different writers as to what is yet known of the nature of this syndrome (p. 656) Further investigation is required before an opinion can be given as to whether the characteristic **spherocytosis** in this form of hæmolytic anæmia is due to some " inborn " disability or abnormality in the functioning of the bone-marrow itself, or is produced by the action of hæmolysins or other toxic agents on **normally-formed** erythrocytes *after* these have been produced by the marrow.

This heredo-familial variety of the disease is chronic in its course, lasting for many years ; and it has been said that the patient is usually " more jaundiced than ill." Such patients are, however, subject to the occurrence of **exacerbations** of the disease, precipitated, it may be, by some accidental or intercurrent cause which acts merely by lowering the patient's state of health and resistance. The anæmia thus tends to occur in " waves " or "**crises,**" during which the total number of the red corpuscles falls rapidly, perhaps to three and a half or three million per c.mm., and is characterised by the presence of a pronounced **reticulocytosis**—up to 50 per cent. or more of the circulating erythrocytes—along with which there are, as a rule, varying numbers of **normoblasts,** these phenomena being evidence of an active **erythroblastic reaction** on the part of the **bone-marrow.** This reaction, as already explained, is probably of the nature of an endeavour of the blood-forming tissues to make good the excessive blood-destruction. The **fragility** of the red corpuscles is increased during the crisis, and experimental hæmolysis or laking (when tested by adding them to a series of graduated dilutions of hypotonic salt-solution) commences at a dilution of 0·75 or 0·7 per cent., and is complete at about 0·4 per cent.—in contrast with the hæmolysis of normal red corpuscles which does not begin as a rule until the dilution has reached 0·45 per cent. (p. 586).

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[1] In this " classification " we have interchanged the words " Anæmia " and " Icterus," and in it, and in the preceding " Table of Hæmolytic Syndromes," we have made a few minor alterations in terminology and spelling. For descriptions of the various types of jaundice see pp. 228–230.

[2] In this connection it must be emphasised that "**hæmolysis**" in the culture-tube and hæmolysis within the living body are by no means parallel processes. Many organisms are labelled as " hæmolytic " and thought to be more dangerous than those which do not hæmolyse red corpuscles *in vitro*—but this is true only to a limited extent and in some instances. Not only certain streptococci, but most of the staphylococci, are " hæmolytic " in this sense, but so are some harmless non-pathogenic organisms such as *Bacillus subtilis.* Some *non*-hæmolytic varieties of streptococci are often none the less dangerous although *not* acting directly upon red corpuscles *in vitro.*

This increase in the degree of the fragility runs parallel with that of the **spherocytosis,** both phenomena being exaggerated during the crisis, and tending to become less pronounced after it has passed. The **spleen** in particular (p. 699) is concerned with the phagocytosis and destruction of these more fragile corpuscles, and the organ itself, already enlarged, becomes still more so during the exacerbation. **Splenectomy** (p. 700), by eliminating the most active agent concerned in the destruction of the fragile corpuscles, ameliorates the condition clinically, but does *not* cure it physiologically, *i.e.*, the corpuscles still to a great extent maintain their spherical shape, and the increased fragility therefore also tends to persist, though in lesser degree than during the crisis itself.

The **spleen,** as just indicated, is as a rule much enlarged, is engorged with blood, and its structure obscured, and, as in various toxic and other conditions, the arterioles often show hyaline degeneration (p. 214, and Plate X, opposite p. 210, Fig. 6).

The **reticulo-endothelial cells** are greatly increased in number and activity, and become loaded with blood-pigment giving the ferrocyanide reaction, and these pigment-laden cells are present also in the **bone-marrow** (*cf.* Plate XVII, opposite p. 616) and in large numbers in the **kidneys** and **liver**. There is abundant excretion of bilirubin in the bile—the formation of gall-stones being common : of urobilinogen (and urobilin) in the urine : and of " coproporphyrin I " in both fæces and urine (*cf.* p. 649).

(B) ACQUIRED TYPES of HÆMOLYTIC ANÆMIA or ICTERUS

1. **Secondary to Known Causes.** *B.* (or *Cl.*) *welchii* produces true hæmolytic anæmia by direct action upon the corpuscles themselves, for example in cases of intestinal obstruction, in which the organisms and their toxins are important factors in bringing about the general toxic symptoms. Occasionally, a severe **infection** with streptococci or staphylococci will produce a hæmolytic anæmia by the direct lysis of the circulating corpuscles by the hæmolytic toxins produced by the organisms. More frequently, however, such infections lead to the production of anæmia by weakening and inhibiting the erythroblastic activity of the bone-marrow.

Malarial parasites, especially those of malignant or subtertian fever (p. 380), may cause destruction of the corpuscles, not only by invading them and feeding upon their contained hæmoglobin, but also by bringing about their acute hæmolysis. In certain cases of malarial infection, an attack of **black-water fever** may supervene, either because the patients are unduly susceptible, or are debilitated by prolonged or repeated attacks of the malaria itself, or by other causes such as alcoholic excess or intercurrent disease. The urine becomes very dark in colour from the presence of **urobilin** and altered **hæmoglobin,** the latter perhaps in the form of **methæmoglobin,** which may also be formed in the plasma of the blood from the oxyhæmoglobin liberated from the corpuscles. The exact nature and mechanism of the hæmolysis, whether due to the action of hæmolysins or other toxic substances, or to a combination of causes including overdosage with quinine or increased susceptibility to its poisonous action, are not yet fully determined (pp. 223 and 227).

Lead-poisoning has been mentioned in the preceding section (p. 655), which deals with anæmias of " nutritional " origin, but is may be noted that, in the more acute and severe cases, the anæmia may be of hæmolytic type and associated with a positive van den Bergh reaction. Excessive destruction of the red corpuscles brought about by the toxic action of lead was well demonstrated in the case of patients suffering from malignant disease who were submitted to treatment with lead-preparations given by intravenous injection. (See also p. 1185.)

Certain drugs such as **phenyl-hydrazine** have been employed therapeutically in polycythæmia (p. 638), in order to utilise their capacity of causing blood-destruction ; whilst in susceptible patients other chemical substances sometimes exhibit a similar action when given for other reasons, for example arsenical compounds for the treatment of syphilis, or potassium chlorate if taken in excess, *e.g.*, for stomatitis, the latter drug being dangerous especially in cases of renal disease. The toxic and other forms of anæmia, *e.g.*, occurring in pregnancy, are mentioned elsewhere (p. 654).

In this group may also be included the acute hæmolysis which results from transfusion with incompatible blood (pp. 589–591) and occasionally following upon the administration of antitoxic and other sera.

2. **Symptomatic hæmolytic anæmia** associated with other grave diseases is mentioned in the various sections dealing with these conditions themselves. That complicating and resulting from malignant disease is described below in the next section (pp. 664 and 667–8).

3. **Acquired Hæmolytic Anæmias of Unknown Causation.** These vary greatly in the degree of their acuteness or chronicity. Their nature has already been partially discussed when dealing with the so-called congenital forms of the hæmolytic syndrome. In some instances it has been thought that what appears to be an independent acute attack may be no more than an exacerbation of an already present but latent condition of spherocytosis, the paroxysm being precipitated by some non-specific exciting or environmental factor such as muscular exertion or exposure to cold. In its more intense forms, the attack of so-called **paroxysmal hæmoglobinuria** may supervene in the course of some other disease, but in certain instances the hæmoglobinuria so dominates the clinical picture that it comes itself to be regarded as a clinical entity. As the name implies, it is characterised by sudden and perhaps repeated attacks of hæmoglobinuria, associated usually with symptoms of vascular disturbance, cramps, pain in back and legs, and possibly rigors, and by the passage of free hæmoglobin in the urine, following upon and due to **intravascular lysis of the red corpuscles.** The blood-count falls rapidly, but, after the paroxysm, the number of the red corpuscles rapidly rises again.

In a certain proportion of the cases, **syphilis** has been thought to be an important factor in the production of the hæmolysis, as is also any undue **exposure to cold.** There is believed to be some direct connection between these two ætiological factors : syphilis with the presence of a hæmolysin in the blood : and the exposure to cold producing the necessary fall in the patient's temperature. In the blood of those subject to such attacks, the presence of a **hæmolysin** capable of reacting both *in vivo* and *in vitro* has been proved experimentally. It reacts as an immune-body or amboceptor, but apparently it can do so only after the temperature is lowered and has been raised again. The experimental test is known as the **Donáth-Landsteiner reaction** and depends upon obtaining a positive hæmolytic reaction with a mixture of the **patient's serum,** the **patient's red corpuscles,** and the necessary **complement**—but only if the tubes have first been kept **in the refrigerator** for half to three-quarters of an hour and *then* incubated for a couple of hours at 37° C. *No* hæmolysis results in controls of the same mixture kept from the first at room-temperature or at 37° C. In the body of the patient, the condition of **chilling** or **exposure to cold** thus appears to constitute the important immediate factor in producing the paroxysms of hæmoglobinuria in this particular variety of the syndrome. Some of the patients thus liable to attacks of paroxysmal hæmoglobinuria have been observed to suffer also from Raynaud's syndrome (pp. 187, 244, 483, etc.), exposure to cold being an important factor in the production of *both* of these conditions.

Another form of **chronic hæmolytic anæmia** is that characterised from time to time during its course by the occurrence of **paroxysmal nocturnal hæmoglobinuria**—the "Marchiafava-Micheli syndrome." Each acute hæmoclastic crisis is here also associated with an attack of hæmoglobinæmia, and there is persistent hæmosiderinuria, moderate enlargement of both spleen and liver with thrombosis of the central veins of the liver and zonal necrosis in the lobules, siderosis of the renal tubules and an erythroblastic reaction of the bone-marrow. It is thought that here again the unduly fragile corpuscles are susceptible to attack by a lysin, this attack being facilitated by the reduced alkalinity (or "increased acidity") of the blood owing to the lowering of the hydrogen-ion concentration during sleep resulting from "decreased pulmonary ventilation." The tendency to these nocturnal exacerbations is increased by administering acid-forming, and decreased by alkaline, salts.

Sickle-cell anæmia is a heredo-familial disorder found mostly in negroes. It is commoner in males, and in it varying numbers of the red blood-corpuscles are of curious shape—the so-called "sickle-cells." Such an appearance can be seen usually only after special fixation of the blood, *e.g.*, with formalin, but is readily demonstrable in preparations of fresh whole blood sealed in shallow chambers with vaselined cover-slips. "Sickling" is, however, now described as present in the blood of some 5 per cent. of *all* negroes, and is not necessarily accompanied by anæmia. The colour-index has been variously described by different writers, in their own particular series of cases, as hypo-, normo-, and hyperchromic. This variety of anæmia is also characterised by the presence of polychromasia and of increased numbers of reticulocytes ; and, in the active stage of the disorder, there is generally an increase in the neutrophil leucocytes of up to 20,000 or more. In the less active stages, bilirubin may be increased in the blood, and urobilin in the urine, and hæmosiderin may be deposited in the spleen and liver.

"**Ovalocytosis,**"[1] so-called, is a somewhat analogous inheritable anomaly in the morphology of the erythrocytes and is found amongst white races, but is not, as a rule, associated with the development of anæmia.

Von Jaksch's Anæmia or **Syndrome : Acute Hæmolytic Anæmia ("of Lederer"**[2]**) :** and **Erythroblastic (Cooley's) Anæmia.** There is considerable doubt as to whether these rare heredo-familial forms of hæmolytic anæmia are distinct diseases of the hæmopoietic organs and tissues or are to be regarded rather as the secondary results of other diseases such as rickets, syphilis or of some gastro-intestinal or other disorder—the result being produced in the blood-forming tissues whilst these are still in an imperfectly developed condition. It is not unlikely that " Lederer's " and von Jaksch's anæmias are respectively the acute and the chronic forms of the same disease, or are at all events closely related to each other.

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[1] "Ovalocytosis" : *see* footnotes, pp. 5 and 641.

[2] Although this has come to be known as "Lederer's anæmia" (1925), it had, as pointed out by Dameshek and Schwartz (p. 657), already been fully described by Chauffard and his collaborators in Paris between 1907 and 1912.

In the **acute hæmolytic anæmia " of Lederer "** or, as it ought to be called, after its original discoverer, **" of Chauffard "**, children of from six months to three years of age are attacked, the illness being characterised by pyrexia and leucocytosis, as well as by a severe grade of anæmia, described variously by different writers as macro-, normo- or micro-cytic and associated correspondingly with a high, a normal or a low colour-index. The cases usually respond well to treatment by transfusion and the administration of iron.

In **von Jaksch's syndrome** (also sometimes called **" splenic anæmia of infants "** or **" anæmia pseudoleukæmica infantum "**—p. 698), an analogous but more slowly developed condition attacks children during the first two or three years of life, the anæmia being at first moderate in degree and associated as a rule with enlargement of the spleen (p. 698), liver and lymph-nodes and accompanied by a pronounced leucocytosis of up to from 25,000 to 40,000 per c.mm. The colour-index, as in the case of the more acute form, varies, and in some instances is recorded as less than normal, but in others a high index, corresponding with the macrocytosis, has been noted. Myelocytes may be found ; and erythroblasts, usually normoblastic in type, are frequently numerous, and macroblasts or even definite hæmoglobinised megaloblasts are occasionally present, with a corresponding erythroblastic reaction in the bone-marrow. As already indicated, the disorder, in contrast with that of the " Lederer " type, is often very chronic. The disease is not necessarily fatal, and recovery may ensue under appropriate treatment, including the administration of iron, suitable dieting, and, if necessary, transfusion.

Erythroblastic or **Cooley's Anæmia** (p. 698) is closely related to the anæmias of " Lederer " and von Jaksch. It also is familial, or at all events " congenital," in character and occurs in children usually under two or three years of age, especially those belonging to races inhabiting the Mediterranean basin. As implied by the name given to the disorder, the special feature of the blood is the presence of large numbers of erythroblasts, along with which are found numerous reticulocytes. A positive van den Bergh's reaction is usually obtained in the blood-serum and a leucocytosis of various types of cell, mostly non-granular, but usually including also myelocytes and metamyelocytes, is present. Hæmosiderosis of the liver, spleen, pancreas and other organs is a pronounced feature, and there are structural changes in the bones—thickening of the skull and increase of the marrow of the diploë. Treatment, *e.g.*, by transfusion, is of less avail than in the other forms of the disease.

In all of these closely allied disorders or syndromes, excessive hyperplasia of the bone-marrow, especially of its less mature erythroblastic elements, is present ; and, in the spleen and liver, nodules or patches of " myeloid transformation "—mainly erythroblastic—have been recorded as having occasionally been found.

It is only right to point out that, owing to the variable blood-pictures which have been recorded as associated with many of these rarer diseases or syndromes, there is considerable justification for doubting the specificity of some of the conditions described in the literature.

III. ANÆMIAS CAUSED BY HÆMORRHAGE

Anæmia from Loss of Blood from any cause, for example in traumatic hæmorrhage, perforation of a vessel by ulceration (*e.g.* in the wall of a phthisical cavity, or in the floor of a gastric or duodenal ulcer), post-partum hæmorrhage, metrorrhagia, hæmaturia, and hæmorrhages from nasal or other mucous membranes. The effects of these, naturally, vary greatly, and the resulting blood-picture will depend upon several factors, the chief of which are the **frequency** and **rate** of the blood-loss and also its **amount** and **duration.**

The immediate danger of a **single large hæmorrhage** is death from lowered blood-pressure (pp. 183–4). A fatal issue may, perhaps, be averted by making up the bulk of the blood by the intravenous transfusion of compatible human blood (pp. 589–591), or, if this should not be immediately available, by the injection of sterile normal-saline solution into a vein or subcutaneous tissues. Where this is not done, and when death does not supervene, the lowered pressure within the vascular system induces rapid transudation of the lymph from the tissues into the vessels, and the total **bulk** of the blood may be comparatively rapidly restored if sufficient fluid is available.[1]

Immediately after an **acute** hæmorrhage the blood-picture is therefore practically unaltered, but, as the blood-volume is thus restored by the addition of tissue-fluids to the remaining total intravascular blood-volume, the counts of the now "diluted" formed-elements fall and the "anæmia" thus becomes demonstrable. The blood is at first, therefore, more watery. Because of the general effect of the loss of blood upon the bone-marrow, that tissue and the other blood-forming organs such as the spleen and lymph-nodes, are then stimulated to take on increased activity in order to replace the various types of lost blood-cells. As has already been mentioned in the section upon blood-formation in the bone-marrow (pp. 614 and 619), when such an erythroblastic reaction is brought about, **all** the hæmopoietic activities of the tissue are stimulated, before the marrow steadies down, as it were, to produce the special type of blood-cells required—in this case more particularly the erythrocytes. A certain amount of leucoblastic activity thus accompanies the erythroblastic reaction for the replacement of the lost red corpuscles, and in this way is explained the occurrence of **post-hæmorrhagic leucocytosis,** as it is called, which is practically a constant phenomenon in such cases, the increase being mainly of the marrow-produced granular leucocytes, chiefly of the neutrophil series. Of these, the mature polymorphonuclear cells are those especially increased, but a varying number of immature cells may also find their way into the circulating blood.

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[1] In this connection, compare and contrast the effects of shock upon the circulation and body-fluids (pp. 183–184).

Even one **repetition** of a large hæmorrhage may greatly retard an otherwise rapid return to normal, or may lead to a fatal issue; whilst **persistent** or **frequently repeated small hæmorrhages,** even when only comparatively slight in amount, from chronic ulcers of the stomach and duodenum, hæmorrhoids, menorrhagia, chronic purpuric conditions, and infestation with hookworms (*Ankylostoma duodenale*) may all give rise to anæmic states of considerable severity, the colour-index being lowered to 0.7 or less.

The recurring hæmorrhages of hæmophilia (p. 670) are another possible cause of this type of anæmia, and such cases usually present little difficulty in their diagnosis, unless, as may happen, the bleeding is internal, for example, within the peritoneal or other body-sacs.

IV. ANÆMIAS DUE TO VARIOUS OTHER KNOWN CAUSES

These were formerly described as "secondary anæmias," but, as explained on p. 640 *et seq.*, we prefer to discard this, as well as the still less appropriate term "idiopathic"—as *all* anæmias must have *some* cause, known or unknown. In addition to anæmias due to the **direct** loss of blood, other causes may lead to much the same results, but **indirectly.** Thus albuminuria, over-prolonged lactation, chronic suppuration, as well as inanition from starvation or from the deficient absorption of food or of special food-elements, including hæmopoietin (p. 647), iron and vitamins (p. 439), or other analogous causes, may in like manner lead to serious anæmia.

Anæmias, varying in degree of intensity, may also **follow acute fevers and allied conditions,** especially if these be prolonged, as in the case of typhoid fever. Similarly, anæmia, sometimes profound, occurs as an **accompaniment** and **consequence of chronic wasting diseases** or "**cachexias**" such as phthisis, syphilis, cancer, malaria (also considered under animal parasites), etc. In several cases which we have ourselves investigated, the patients suffered from profound anæmia, diagnosed clinically as "pernicious" in type, but in which, on post-mortem examination, innumerable minute **miliary tubercles** were found throughout the entire bone-marrow (*cf.* p. 68). In two of these there was slight old pulmonary tuberculosis, in one case subacute tuberculous peritonitis, and, in another, some chronic glandular lesions. We describe later (in the footnote on p. 668) a somewhat analogous condition of profound anæmia in a young man of twenty-two, from whom a small pyloric carcinoma had previously been removed. No secondary growths were found at the operation, but, on post-mortem examination, the entire bone-marrow was found to be closely studded with innumerable **secondary carcinomatous nodules**—a state which may be described as **carcinomatosis**—and the intervening marrow-tissue showed advanced gelatinous degeneration. No secondary growths were discovered in any of the other organs or tissues.[1] **Chronic poisoning** by means of lead, arsenic, mercury, sulphuretted hydrogen, carbon disulphide, T.N.T. (pp. 245, 771 and 777), and analogous substances, may produce a severe type of anæmia (*cf.* p. 660). Anæmias of all grades, up to profound aplastic anæmia, may result from repeated or prolonged exposure of the bone-marrow to the more penetrating varieties of **X-rays.**

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[1] For some further details of this case, *see* footnote on p. 668.

Blood-destruction and regeneration have also been studied extensively in **anæmias artificially produced** by the inoculation of animals with phenylhydrazin, saponin, bacterial toxins, tapeworm-extracts, hæmolytic sera (pp. 657 and 661), and the like.

Some of the most profound degrees of anæmia known, and frequently simulating untreated "pernicious" anæmia in type, are those produced by **certain animal parasites,** especially *Ankylostoma duodenale* (p. 411–2), *Diphyllobothrium latum* (p. 406), and, in rarer instances, *Trichuris trichiura* (p. 416) and *Enterobius* (*Oxyuris*) *vermicularis* (p. 409). The observation that anæmia of this profound nature is not by any means an invariable accompaniment of such infections, and that the symptoms produced by the presence of the three last-mentioned of these intestinal parasites are often comparatively slight in degree, has led to the supposition that—for example in cases of infestation with *Diphyllobothrium*, where the resulting anæmia is of a profounder type—it is produced by some **superadded morbid condition of the parasite itself,** whereby certain toxic substances are produced by it within the intestine of its host, from which they are absorbed and thus come to produce their effects. We might also speculate upon the possibility of some damage to, or interference with, the activities of the argentaffine (or argyrophil) cells of the gastro-intestinal tract (p. 648), but recovery, in such cases, may follow upon expulsion of the parasite, provided the anæmia has not already become too profound. Further investigation of these points is required before a definite opinion on them can be given.

Some **blood-parasites,** notably those of **malaria,** can produce serious anæmia, partly from their feeding upon and partly from using up the hæmoglobin of the red corpuscles which they infest, and thus bringing about the increased destruction of the corpuscles, as well as from the action of certain toxins produced by the parasites (p. 381 *et passim*).

Methods by which these various causes of Anæmia may act. (i) **Diminished Nutrition.** There may be interference with the digestive and assimilative capacities of the patient, or his food or some of its essential elements may be insufficient to supply material and energy for the hæmopoietic functions of the marrow and other blood-forming tissues (for details regarding the various hæmopoietic factors concerned, *see* pp. 647–8). (ii) **Diminished Activity on the Part of the Blood-forming Organs themselves** is an important factor, and may be produced by the action of bacterial and other toxins, or chemical poisons such as lead, arsenic, mercury or alcohol. (iii) Again, **Over-Activity of these Tissues** in one direction, for example in the production of leucocytes of the granular series, as is seen in diseases characterised by leucocytosis, may lead to a corresponding **diminution** in the output of cells of the red series. Prolonged over-activity, from whatever cause, may also lead to **exhaustion** of the hæmopoietic tissues and consequent failure of their blood-forming powers. (iv) Or again, **diseases such as Syphilis,** which lead to degenerative changes in these organs, may cause a progressive **atrophy** and **failure of their functions.**

(v) **The Increased Destruction of fully-developed Blood-Cells,** in the blood-plasma, spleen, liver, bone-marrow, or elsewhere, whether brought about by the mechanism of hæmolysis (solution of the red cells), of phagocytosis, especially by cells of the reticulo-endothelial system, or by any other cause, is, of course, an obvious factor in the production of anæmia. Increased fragility of the corpuscles themselves, from changes in their shape (spherocytosis) and other causes is discussed on pp. 586–7 and 655–9. Actual loss by hæmorrhage has already been discussed ; whilst other causes are the increased consumption of the albumins of the blood and tissues in fevers and similar conditions : or, as already mentioned, the constant leakage of albumin in albuminuria (in addition to the action of retained toxic substances).

Changes in the Tissues in Anæmias. When the anæmia attains a certain degree of severity, varying in different individual patients and in different types of disease, there may occur **multiple hæmorrhages,** varying in size from **petechial**[1] (*e.g.*, in the retina or in the subserous or submucous coats in various positions), up to **profuse hæmorrhages,** especially from mucous membranes. The occurrence of **dropsy** is a common phenomenon. In the hæmolytic organs, especially the liver, spleen, and bone-marrow, there may be evidence of the **excessive blood-destruction** in the form of **pigment,** usually contained within phagocytic cells, mostly, as already noted, of the reticulo-endothelial system (pp. 381 and 616, and Plates XI and XVII, opposite pp. 222 and 616). This pigment is most commonly in the form of **hæmatoidin ;** but iron-containing pigment or **hæmosiderin** may also be present, especially in advanced cases, though not, as a rule, in such quantity as is seen in untreated anæmias of Addisonian type.

Blood-changes in Anæmias. These naturally vary considerably with the cause, duration, and degree of intensity of the change, and also with the capacity of the hæmopoietic tissues to undertake increased erythroblastic activities. If the loss of blood has been sudden, *e.g.*, by hæmorrhage, and not repeated, there may be fairly rapid re-formation of blood, especially of its fluid constituents. The **red corpuscles** in anæmias may show abnormalities in size (**anisocytosis**) and shape (**poikilocytosis**), which, in the less severe types of the disease, may be slight, or which may be pronounced when the condition is more intense. In severe cases, **nucleated reds** or **erythroblasts** tend to appear, owing to the vascular and proliferative activity in the bone-marrow (erythroblastic reaction). In the cases of miliary tuberculosis and carcinomatosis of the bone-marrow, to which reference is made on p. 664, large numbers of erythroblasts were present. The nucleated red cells thus occurring in the blood in the severer types of anæmia frequently show fragmentation of their nuclei, and it is not uncommon to find such cells with nuclei which are somewhat larger and paler, *i.e.*, developmentally less mature, than those of the ordinary normoblast ; whilst, in certain cases, *e.g.*, in *Diphyllobothrium* anæmia, as already mentioned, the changes in the red corpuscles may closely resemble, and be practically indistinguishable from, those observed in untreated

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[1] From the word "*petechiæ*," small livid or purple spots (like flea-bites), from Low Latin *peteccia*, through the Italian *petecchia*, from Latin *petigo*, an eruption, *cf. impetigo*.

Addisonian anæmia, *i.e.*, poikilocytosis, the presence of megaloblasts and megalocytes, etc. (pp. 649–650).

The **leucocytes,** for the reason already mentioned, may be temporarily increased in numbers after hæmorrhage ; and, in other instances, leucocytosis, if present, may be due to the diseased condition producing the anæmia. The special types of leucocyte involved will, therefore, in such cases, depend upon the nature of the cause at work.

The **blood-plates** may be greatly increased after hæmorrhage—perhaps to three or four times their normal number (601–2).

V. ANÆMIAS OF UNKNOWN CAUSATION

Strictly speaking, many cases of anæmia should be considered in this category, but may provisionally and conveniently be classified as " hæmolytic " or " nutritional " on account of some especially prominent clinical feature.

Progressive Primary Aplastic Anæmia is a rare disease of which less than 200 cases have been recorded. The bone-marrow becomes exhausted at an early age without any apparent cause, since in many of the recorded cases the patients have been under the age of forty years and without previous history of blood-disease or abnormality. Some writers have ascribed the condition to premature senility of the bone-marrow, and certainly it corresponds with this most closely. Such cases need great care in their diagnosis, for the commonest examples of aplasia are those which follow previous hæmopoietic disturbances, particularly Addisonian anæmia. In " primary " aplasia, the anæmia becomes progressively more severe and the leucocytes of the blood diminish along with the red blood-corpuscles, which may fall to under 1,000,000 per c.mm. The colour-index is usually less than 1·0, and, though periods of attempted blood-regeneration may be seen in the earlier stages of the disease, these become progressively less efficient and ultimately cease to occur. Blood-transfusion is generally regarded as the only possible form of treatment when such " aplasia " has occurred, but transfusion will be needed more and more frequently as the disease progresses, and the fatal issue is merely postponed by the treatment.

THE BLOOD IN GENERAL DISEASES

The condition of the blood in the Acute Infective Fevers, and in Septicæmias and similar infections, has already been sufficiently described under Leucocytosis and the Reactions of the Hæmopoietic Tissues, especially the Bone-Marrow. For a fuller account of such changes, and the alterations found in the blood in general diseases such as Myxœdema, Exophthalmic Goitre, Tuberculosis, etc., special works on Hæmatology should be consulted.[1]

BLOOD-CHANGES IN MALIGNANT DISEASE

Neoplasms as such do not appear to lead to any specific or important changes in the blood-picture other than those due to the **secondary** effects of sepsis or of interference with nutrition and function from the position of the tumour in the body. It is, therefore, in the present state of knowledge, not possible to make a diagnosis of malignant disease from the results of the blood-examination alone, although these may help in coming to a decision when considered along with the rest of the clinical findings.

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[1] L. E. H. Whitby and C. J. C. Britton, " Disorders of the Blood," 4th ed., 1942.

With **malignant** growths, some degree of anæmia is usual when the tumour has reached any considerable size or if **metastasis** has occurred. If there has been the occurrence of profuse or repeated **hæmorrhage** from the tumour, as, for example, in carcinoma of the stomach or bowel, the changes in the blood usually found in cases of hæmorrhage will be present (p. 663).

Leucocytosis of moderate degree will occur where there is bacterial infection of the tumour-substance or where hæmorrhage has taken place, and also in certain cases where the liver is involved by metastases or where there is involvement of the bone-marrow by secondary deposits.

In certain cases of "**carcinomatosis**" **of the bone-marrow,** *i.e.*, widespread secondary involvement of the marrow throughout perhaps every bone in the body, such as sometimes supervenes in carcinoma of the stomach,[1] a profound degree of anæmia may occur, characterised, in a proportion of the cases, by the appearance in the circulating blood of considerable numbers of nucleated red corpuscles—sometimes sufficiently numerous to be described as an "**erythroblastæmia,**"[2] or, when accompanied also by immature cells of the neutrophil leucocyte-series, as "**leuco-erythroblastæmia.**" In the earlier editions of our textbook, 1908 and 1921, we pointed out the occurrence of this phenomenon of **erythroblastæmia,** not only in **carcinomatosis,** but also in patients suffering from **diffuse miliary tuberculosis** of the bone-marrow. These observations were made on cases investigated previous to 1905.

PURPURA and other HÆMORRHAGIC DISORDERS

"**Purpura**" is symptomatic of many differing diseases, in which hæmorrhages of varying degree occur from or into the skin, mucous and serous membranes and, in some instances, into the tissues and organs themselves. These hæmorrhages are often of **toxic** or **infective** origin, as in the severer types of streptococcal infection and in cerebrospinal or "spotted" fever (p. 981). Or, again, the cause may be some well-defined "**blood-disorder**" such as a leukæmia.

There remain, however, certain examples in which no as yet demonstrable causative factor appears to be present; and these, although they represent a consecutive series differing only in degree, may be divided into two groups—**purpura simplex** and **purpura hæmorrhagica.** The former is often a comparatively mild condition: but the latter tends to be more severe and is often fatal and associated with an abrupt fall in the number of circulating blood-platelets —a **thrombocytopenia**—(pp. 669 and 699). When these fall below 50,000 or

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[1] Reference is made on p. 664 to a case of pyloric carcinoma of this nature in a man of twenty-two years of age, in whom, a few days before death, there was an **extreme degree of anæmia**—under a million red corpuscles per c.mm., large numbers of them **nucleated**—and, as already noted, at the post-mortem the marrow of the femur, humerus, ribs and vertebral bodies was found to be studded throughout with innumerable small nodules of the carcinoma. (Carnegie Dickson, 1908, *loc. cit.*, *The Bone-Marrow*, Appendix I, p. 145, Case No. 22.)

[2] "Erythroblastæmia and its Value in the Diagnosis of Neoplastic Infiltration of the Bone-Marrow," by F. Parkes Weber, *Lancet*, 1940, i, 1077.

40,000, purpura is likely to supervene, and in serious cases they may be as few as 10,000 per c.mm.—whilst, in those cases of purpura in which there is no obvious deficiency in their number, they may be altered **in quality.** The **bleeding-time** is usually prolonged, but coagulation is not necessarily unduly delayed (p. 587 *et seq.*).

There is considerable probability that such purpuric symptoms are, in some instances, due to certain **changes in the vascular endothelium**—associated, it may be, with **vitamin-P deficiency**, *i.e.*, an inadequate supply of flavones (citrine)—together with some abnormality in the bone-marrow, probably a diminution in the numbers or some interference with the functions of the large mononuclear giant-cells or **megakaryocytes** from which the platelets are derived (Fig. 361, p. 601) : or perhaps failure in the process of maturation of the platelets themselves, or increased resistance or other abnormality in their composition.

THROMBOCYTOPENIA : ESSENTIAL AND SYMPTOMATIC

Thrombocytopenia, or deficiency in the number of blood-platelets in the circulating blood, may be " **Primary** " or " **Essential** ", and " **Secondary** " or " **Symptomatic** ". Pathological conditions due to alterations of the blood-platelets may be caused by **abnormalities in their number** *or* **in their quality,** and may be associated with deficient production of them by the megakaryocytes of the bone-marrow, and these may themselves be either normal or reduced in numbers (pp. 601–2) : or with increased destruction of the platelets by the reticulo-endothelial system, especially of the spleen (pp. 699 and 700–1), whether this be due to abnormal fragility of the platelets themselves, or to increased phagocytic activity on the part of the spleen.

Essential thrombocytopenia (**Werlhof's disease,** or **thrombocytopenic purpura hæmorrhagica**) (p. 588) is characterised by the occurrence of hæmorrhages into the skin and internal organs or from mucous membranes : the bleeding-time being prolonged, sometimes excessively : the coagulation-time delayed : and retraction of the blood-clot outside the body delayed and imperfect. Unlike hæmophilia, the disease occurs in females more frequently than in males—more especially in girls during menstruation and leading in them to the occurrence of menorrhagia—and frequently in children as well as in adolescents and young adults.

The platelets are often not only deficient in number but abnormal in size, with the presence in the blood of forms both larger and smaller than normal. Amelioration of the acute condition is usually obtained, even if only temporarily, by blood-transfusion. Opinion differs as to the value of splenectomy (pp. 700–1), but, if this is contemplated, the additional preliminary treatment by transfusion as a precautionary measure is advisable, in which connection see also under " Coagulation and Thrombosis " on pp. 161 to 163 : and note upon Vitamins K and P on pp. 442–3 respectively.

Every one performing many vein-punctures is familiar with the phenomenon, seen in a certain proportion of patients, of the production of **petechial hæmorrhages** in the skin of the forearm when the pressure-armlet is tightened, indicating the presence of increased permeability or fragility of the capillary-walls—noticeable, for example, in cases of focal streptococcal infection and in various so-called "blood-diseases"—as well as in the thrombocytopenic cases under discussion. Although crude extracts of normal human spleens produce some fall in the number of platelets when injected into rabbits and other animals, a still more pronounced reduction in the platelet-count has been obtained with extracts of the spleens of patients who have suffered from thrombocytopenic purpura.

Non-thrombocytopenic purpura occurs in what has been termed "anaphylactoid" purpuras, such as the conditions named after **Henoch** (p. 739) and **Schönlein** (so-called "purpura or "peliosis rheumatica"). Factors which do *not* appear to have any very important bearing on the production of purpura are high blood-pressure; anæmias as such (?); and nephritis, unless uræmia is present (Stanley Davidson, 1938).

HÆMOPHILIA, or "HÆMORRHAGIC DIATHESIS"

Hæmophilia was first described by John Otto in 1803 in a paper entitled "An Account of an Hæmorrhagic Disposition Existing in Certain Families." [1] Persons who suffer from this disease—or "bleeders," as they are popularly called—are usually young males who are hereditarily predisposed to the occurrence of hæmorrhage, which may be severe, and even fatal, and may arise from the most trifling injury, such as a slight blow, a scratch or small cut, or the extraction of a tooth,[2] or even sometimes without any obvious exciting cause. This tendency to bleeding in these cases is increased by the presence of any of the usual causes of hæmorrhage, *e.g.*, any septic lesion. Most of the deaths from the disease occur in adolescence and before the age of twenty-one. The coagulation-time of hæmophiliac blood is lengthened—sometimes greatly so. Many hypotheses have been advanced as to the reason for this delay, and the mechanism by which the coagulation of the blood is postponed or prevented. According to many recent observers, mostly, however, merely confirming the work of T. Addis [3] in Edinburgh thirty years ago, hæmophilia appears *not to be due* to any *quantitative* deficiency in the various constituents of the blood, including prothrombin (and thrombin), fibrinogen (and fibrin), blood-platelets, or thromboplastin (thrombokinase), or calcium, all of which are as plentiful in hæmophiliac as in normal blood. Addis, and many writers who have followed him, believe that there is some **qualitative defect in hæmophiliac prothrombin** resulting in its delayed activation and development into thrombin. One explanation of this is that the **platelets,** although as numerous as in normal blood, are unduly "stable," and therefore do not break up sufficiently readily to form thromboplastin—though they can still "conglutinate" efficiently over any small injury in the walls of the small blood-vessels, and hence the capillary bleeding-time is *not* prolonged, as it is in thrombocytopenia (*see* p. 669, and also pp. 587–9 and 601–2.)

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[1] *The Medical Repository*, New York, 1803, **6**, 1.

[2] "Asphyxia following Dental Extraction in a Hæmophiliac," by C. L. Endicott, J. H. Mitchell and G. Qvist, Eastman Dental Clinic, London, *Brit. Med. Jour.*, 1942, *ii*, 34.

[3] "The Pathogenesis of Hereditary Hæmophilia," *Jour. Path. and Bact.*, 1911, **15**, 427. The main conclusions of this writer were that "there is a defect in hæmophiliac prothrombin which reveals itself in the longer time it requires for the change into thrombin, in the presence of thrombokinase and calcium (neither of which is in diminished amount), and this qualitative defect in the prothrombin is the cause of the delay in the coagulation of hæmophiliac blood." He also stated that "There is no appreciable difference in the anti-thrombin content (now known as "heparin" in its various purified forms) of hæmophiliac and of normal bloods." And "there is no substance in hæmophiliac blood, not present in normal blood, which hinders the formation of thrombin. There is no appreciable difference in the amount or activity of the calcium in hæmophiliac and in normal bloods."

The manifestations of the disease, as stated above, are found especially in males, but the disease is transmitted by the mother, who does not herself suffer from its ill-effects. The direct male offspring of a hæmophiliac father thus does not show the symptoms of the disease, which is transmitted by his daughters to his grandsons. Many suggestions as to preventive and prophylactic measures have been made, and of these the transfusion of compatible human blood, repeated if necessary, has been most effective. The injection of extracts of blood-platelets, of placental tissue and other organs, the serum of the horse and other animals, and of various foreign proteins including white-of-egg, calcium salts, vitamins (including vitamins K and P, pp. 161, 442 and 669), and dilutions of snake-venom, have all been tried and had their advocates. When blood-transfusion fails, the advisability of splenectomy may be considered, but is not without its dangers and has not been uniformly successful. Beyond a slight diminution in the number of the leucocytes, especially the polymorphonuclears, noted by Wright, no characteristic microscopical changes in the blood or organs have yet been demonstrated. The hæmorrhages may occur into or from many of the body-tissues, but more especially in and between muscles, and into the subcutaneous tissues and joints (p. 1241–2). They may lead to the production of anæmia (p. 664).

SCURVY, OR SCORBUTUS

This is a vitamin-deficiency disease, characterised by the development of severe anæmia, unaccompanied by leucocytosis, unless from the presence of some inflammatory or other complication. For a description of the more important changes in this disorder, *see* p. 443, and *cf.* p. 1218 *et passim.*

(NOTE.—Certain disorders of the blood, characterised especially by changes in the **Spleen,** are described in Chapter XX, p. 688 *et seq.* **Agglutination** (pp. 131 and 589) **and Hæmolysis** (p. 132), **etc., of red corpuscles,** and analogous phenomena, are dealt with in Chapter V on **Immunity.** The problems connected with **Thrombosis** are also considered under **Thrombosis,** p. 161 *et seq.* Other cross-references to descriptions of individual diseases are given throughout the foregoing chapter itself.)

CHAPTER XIX

DISEASES OF THE LYMPHATIC SYSTEM

SECTION I

SEROUS MEMBRANES

Diseases of these structures are described under their respective systems (*see under* **Pericardium, Pleura, Peritoneum,** etc.).

SECTION II

LYMPHATIC VESSELS

Lymphangitis, or inflammation of lymphatic vessels may be acute or chronic. In the **acute** condition, resulting usually from infection with pyogenic organisms, especially streptococci, the inflamed lymphatics are seen in the skin, *e.g.*, of the arm—in an infected wound, say, of the finger—as narrow, bright red, more or less straight lines, running from the focus of infection towards the nearest groups of lymph-nodes—in this instance the epitrochlear and axillary. The changes in and around these vessels are very similar to those seen in inflammation of veins, viz., inflammatory swelling of the intimal endothelium and the other coats of the vessels, leucocyte-infiltration and œdema of the surrounding tissues (peri-lymphangitis), and, perhaps thrombosis of the lymph in the lumen of the vessel. Not infrequently, however, lymph-nodes become infected, and perhaps suppurate, *without* any obvious involvement of the lymphatic vessels intervening between them and the peripheral lesion, which may, in some cases, be inconspicuous. The proliferating cells of the endo- and peri-thelial coats of lymphatics are regarded by most writers as an important source of the large mononuclear cells of exudates in many inflammatory conditions. Long-continued or repeated attacks may lead to chronic lymphangitis, a condition which is seen in an exaggerated form in elephantiasis (pp. 424–7).

Chronic lymphangitis is often due to some specific infective agent, especially the micro-organisms of tuberculosis, syphilis and glanders. When the subperitoneal lymphatics and lacteals have become infected, say, from a tuberculous ulcer of the intestine, they become prominently marked out as whitish lines dotted with small granulations of tuberculous lymphangitis. In glanders, the lymphatic trunks especially are affected, and show as thickened cord-like swellings—the so-called " farcy-pipes " seen in the horse.

Lymphangiectasis. Congenital lymphangiectasis or dilatation of lymphatics may occur in various forms, *e.g.*, in a circumscribed form in lymphangiomas (pp. 332–3), or in the diffuse variety affecting the tongue (macroglossia), lip (macrocheilia), or vulva.

In its **acquired** form, the condition seldom arises from obstruction of the flow in the lymphatic channels. In cases of filarial infestation, however, the presence of the adult worm, *Wuchereria* (*Filaria*) *bancrofti*, may produce an irregular varicose condition of the lymphatics of the groin, pelvis, and abdomen; or the impaction of the prematurely discharged embryos or coiled-up larvæ of the parasite may lead to widespread obstruction of the smaller lymph-channels, this—along with recurring inflammatory attacks—producing the condition of elephantiasis (p. 425 and Figs. 240 and 241, p. 426). Rupture of the diseased lymphatics leads to the escape of chyle, giving rise in such filarial infestations to chylous ascites, chyluria, or chylocele, according to the site of rupture (p. 425). Chylous ascites may also arise occasionally from the pressure of tuberculous glands upon the receptaculum chyli, or ulceration extending into the thoracic duct from a tuberculous focus in its neighbourhood.

Dilatation-cysts, usually minute in size, are very common upon the lacteals in the intestinal wall or mesentery, and may be recognised by their milky, fluid contents.

New Growths. Primary tumours of lymphatic vessels are rare. They are usually congenital, and may occur as plexiform, or, less rarely, as cavernous, **lymphangiomas,** *e.g.*, in the skin and subcutaneous tissue, or, very occasionally, in the ovary or hilum of the kidney (pp. 332–3). They may be combined with adenomatous tumours, *e.g.*, in connection with the parotid, pituitary, and other glands. Cystic tumours of lymphatics or hygromas may be found about the neck and face. Cystic or pseudo-cystic formations may also occur in connection with certain serous membranes, *e.g.*, the so-called "**ganglia**" developing in the neighbourhood of the synovial membranes of joints or tendon-sheaths, especially of the hand or wrist (p. 1253)

Secondary infiltration along lymphatics is common in the case of malignant tumours, especially carcinomas, including malignant melanomas (pp. 323–4).

SECTION III

LYMPHATIC NODES

The lymphadenoid tissue of the body is found, not only in the form of lymph-nodes, but also in the Peyer's patches or aggregated lymphatic nodules and solitary follicles of the intestine, lymphoid tissue of the tonsils and pharynx, the bronchial lymphoid sheaths, periarterial lymphoid tissue of the spleen (Malpighian bodies and ellipsoids), and mesentery and also in the thymus gland before it undergoes involution.

Practically all the lymphatic trunks draining the tissues of the body pour their contents into the lymph-nodes, which are arranged usually in groups. These act as filters for the lymph as it passes through them into the efferent vessels, and they are therefore specially liable to infection by bacteria or other infective organisms carried in the lymph, as well as to the deposit in them of tumour-cells, and of pigment or other particulate substances brought to them in the same way.

The afferent lymphatics, before entering the substance of the node, break up into a fine network upon its surface. From this, the lymph is carried by delicate channels into the lacunar system of lymph-sinuses in the cortex, and then through a similar network in the medulla, from which it is collected by several channels which unite in the hilum of the node to form the efferent lymphatic vessel. Micro-organisms, tumour-cells, and particulate substances brought by the lymph-stream are thus liable to be caught especially in the surface plexus, in the sinuses of the cortex and medulla, or in some other part of the filtering system ; whilst similar substances brought by the blood-stream are more likely to affect the lymph-follicular system of the lymph-node, on account of the fact that the arteries, after entering the node and running in the trabeculæ, are distributed mainly to the lymph-follicles of the organ. For this reason, the lymph-follicular tissue is also very readily affected by anything causing hyperæmia of the nodes, and by inflammatory, septic and toxic conditions acting through the blood-stream. The reticulum of both the lymph-adenoid and the sinus systems is closely associated with cells in varying degrees of development and differentiation. The cell-margins are indefinite, but pale ovoid nuclei with a thin layer of cytoplasm completely ensheath the fibres, and it is thought that these nuclei belong to a cellular syncytium covering the branching and anastomosing fibrils of the reticulum—hence the descriptive term "reticulo-endothelial" applied to this system of cells which readily react in certain pathological conditions (*see* p. 1262) and are actively phagocytic to effete red corpuscles, micro-organisms and foreign particles, *e.g.*, of carbon. In the lymphadenoid areas (lymph-follicles or cords), the meshes of this reticulum are occupied by the closely-packed lymphoid cells or lymphocytes. Lymph-nodes are radio-sensitive and undergo atrophy on prolonged exposure to X-rays. Lymphadenoid tissues require an adequate supply of vitamin B in the diet for the proper maintenance of their functions.

Atrophy of lymph-nodes and of lymphoid tissue throughout the body is associated with the diminished metabolism of old age. Similar but localised atrophic changes are found in the Malpighian bodies and ellipsoids of the spleen, in the Peyer's patches (aggregated lymphatic nodules) and solitary lymphoid follicles of the intestine, and in lymphoid tissue elsewhere. The lymph-nodes become smaller and firmer, and show fibrosis and decreased activity in the production of lymphoid cells, though their bulk may be partly maintained by the infiltration of certain areas with fat—a phenomenon which may be observed not infrequently in lymph-nodes in the neighbourhood of malignant growths quite apart from any associated infiltration with malignant cells, the obstruction of lymphatic channels by new growth accounting for the atrophy of the nodes under these conditions. Atrophy of the lymphadenoid tissues, in association with atrophy of other tissues, is seen in many wasting conditions and is often a pronounced feature in marasmic infants and children.

Amyloid Degeneration. Apart from their involvement in generalised amyloid disease, the lymph-nodes themselves may be the local seat of this change (p. 210). In either variety, they may, to the naked eye, show little apparent alteration and require microscopical examination after treatment with special staining reagents ; or they may present a pale, whitish, shining appearance on section, with small translucent points which stain dark-brown with iodine. The change is usually most pronounced in the connective tissue around and in the walls of the arterioles and the capillaries arising from them. It is best seen, therefore, at the centres of the lymph-follicles, where these vessels are situated. The affected structures show the usual homogeneous swelling and the characteristic staining reactions with methyl-violet (p. 209).

PIGMENTATION. Foreign particles, such as blood-pigment, carbon-particles and stone-dust, may be carried to, and deposited in, lymph-nodes, which, as already explained, act as filters for the lymph-stream. These particles are taken up by polymorphonuclear or mononuclear phagocytic cells in the area drained by the lymphatics and are carried to the nodes of that drainage-area. These cells may either deposit their contained particles in the lymph-node, or may themselves, along with their contents, be englobed by the actively phagocytic reticulo-endothelial cells lining the lymph-sinuses. Such particles are deposited, first in the peripheral network of afferent lymphatics on the surface of the node, then in the lymph-sinuses of the cortex and of the medulla. They may at a later stage also be found in the lymphoid follicular tissue of the cortex ; and, lastly, the whole tissue may be closely packed with pigment. The commonest form of such pigmentation is to be seen in the bronchial nodes, to which particles of carbon inhaled into the lung are carried. A considerable degree of such pigmentation is present in practically all town-dwellers, but it occurs in its most exaggerated form in anthracosis or coal-miners' disease

(p. 543), in which the pigment is carried from the lung, not only to the bronchial, but to the mediastinal and abdominal, nodes, and, in extreme cases, may be found in practically all the lymph-nodes of the body, as well as in the spleen, liver and even the bone-marrow.

Particles of stone and other substances (p. 543 *et seq.*) may be found under similar circumstances, and a pronounced degree of fibrosis in association with pigmentation is found in cases in which, over long periods, silica or foreign particles containing any admixture with silica, such as flint, quartz and ceresite or asbestos (p. 547), are inhaled. In tattooing, a large part of the pigment introduced under the skin is carried by phagocytic cells to the neighbouring lymph-nodes. In the same way, large quantities of blood-pigment may be found in nodes near hæmorrhages or wounds.

When pigmentation of the follicular tissue occurs, the particles are often deposited in it and found free, as in the case of the iron-containing pigment derived from broken-down blood in the case of the spleen or hæmolymph-nodes in chronic malaria.

The presence of pigment leads to proliferation of the reticulo-endothelial cells of the sinuses, and to progressive thickening of the reticulum, apparently from defective nutrition due to interference with the functions of the investing cells which govern the nutrition of the fibres. These changes in the adenoid reticulum and its cells lead to compression-atrophy of the lymphoid cells, and may end in complete fibrosis of the whole lymphadenoid tissue.

LYMPHADENITIS. Acute inflammatory changes are common in lymph-nodes, as these structures are, from their anatomical position and functions, liable to become affected by septic irritants, whether toxins or the organisms themselves ; and, in many cases, both these factors are at work. Such irritants may be carried to the nodes either by the lymph-stream or by the blood ; and, in each instance, the lesions will differ somewhat in accordance with the differing distribution of the lymphatics and of the blood-vessels. Thus, irritants brought by the latter will act first upon the lymphoid follicles, causing hyperæmia, swelling and softening ; whilst the sinus-system will be most affected where there is infection by way of the afferent lymphatics. Bacteria reaching the nodes by these channels tend first to infect the surface plexus of lymphatics, then the sinuses of the cortex and of the medulla, and, lastly, the lymphoid tissue itself. In the majority of infections, however, all the structural elements of the nodes are affected together, though in varying degree. Inflammatory processes often spread to the peri-nodal tissues, and neighbouring nodes may then become matted together by an œdematous and gelatinous-like inflammatory material.

In **acute lymphadenitis,** whether due to soluble toxins or to organisms, there is distinct, and sometimes great, swelling of the nodes—varying considerably, however, with the nature of the irritant. Softening, and, in extreme cases, necrosis, of the adenoid tissue may occur. In the earlier stages of the inflammation, there is at first hyperæmia, showing as small points of congestion corresponding to the lymph-follicular cords, but later becoming more diffuse, with a pale rose-pink tint, which, however, rapidly tends to pass off—*e.g.*, in a few hours—as the adenoid tissue becomes swollen and packed with cells.

Fibrin may be present in considerable amount. In intense cases, hæmorrhages may occur. These may be punctiform or, in some instances, diffuse—*e.g.*, in the bronchial lymph-nodes in **woolsorters' disease** (p. 505). Where hæmorrhages do not occur, the colour of the inflamed nodes rapidly becomes paler, their whole structure becoming crowded with cells—lymphocytes, proliferated cells from the endothelial and perithelial coats of the lymphatics and sinuses, and polymorphonuclear leucocytes. In some cases, *e.g.*, in typhoid fever, the causal organism may be found in the mesenteric nodes ; whilst in the various infective conditions streptococci and staphylococci may be present in cervical, inguinal or other lymph-nodes. In **bubonic plague** enormous numbers of the bacilli are to be seen closely packed and completely filling the lymph-sinuses, from which they can be obtained during life by puncture. These enlarged nodes or buboes are found first, as a rule, in the groin, less frequently in the axilla or elsewhere, according to the original site of inoculation—usually the bite of a flea. The resulting intense inflammatory reaction and swelling is generally hæmorrhagic in character, and spreads to the surrounding tissues, matting the nodes together. In **soft sore** or **soft chancre** (p. 911), buboes often occur in the inguinal lymph-nodes, and Ducrey's bacillus, with or without superadded pyogenic bacteria, may be obtained by puncture of the enlarged node, but not infrequently the organism disappears rapidly as a result of phagocytosis.

In those cases of lymphadenitis in which the inflammation has not been too severe, gradual resolution occurs ; but usually some degree of enlargement and induration persists ; and, especially if there have been repeated acute attacks, a chronic fibroid condition, with atrophy of the lymphoid cells, supervenes.

The presence of pyogenic bacteria may lead to suppuration, commencing as minute purulent foci, which may become confluent and lead to the formation of an abscess, confined to one, or to a fused group of nodes : or spreading to the surrounding tissues, and, if on the surface or near a cavity, usually rupturing and discharging its contents.

Chronic lymphadenitis may be due to long-continued irritation. Apart from tuberculosis and syphilis, it may result from recurrent acute attacks, or be due to the presence of pigment (*see above*). The lesion is then practically always a chronic fibrosis with atrophy of the cellular elements. Where calcification occurs, chronic tuberculosis is the commonest antecedent lesion.

Tuberculosis of Lymph-Nodes (*see under* Tuberculosis, p. 68).

Syphilitic Lymphadenitis (*see under* Syphilis, p. 80).

HODGKIN'S DISEASE,[1] **LYMPHADENOMA or PRIMARY FIBRO-MYELOID MEDULLARY RETICULOSIS** (pp. 123, 695 and 1262–4). As old assistants of the late Professor W. S. Greenfield, we associate ourselves with the statement of Sir Robert Muir : "that the description (of Hodgkin's disease) now given by writers is essentially the same as that first given by Greenfield many years ago. It is well that this fact should be mentioned, as it is generally overlooked by writers on the subject." [2]

In a typical case, there occurs a progressive enlargement of the lymph-nodes, beginning usually in the cervical, or, less commonly, in the inguinal, axillary, or some other group. This enlargement may commence on one side, spread progressively to the opposite side, and to the other lymph-nodes and lymphoid tissues of the body, though, in certain instances, the condition may remain localised in one set of nodes for a considerable time. At some period, varying in individual examples, though sometimes comparatively late, the spleen becomes affected, and mild irregular pyrexia is usually present. In the earlier stages, the blood shows comparatively little alteration, but, as the disease advances, a progressive form of anæmia is established. Variations in the numbers of the white cells are not specially characteristic, and, though in some instances they are distinctly diminished, in many others they have been increased. The occurrence of eosinophilia has been stressed by some writers, but this has not been a constant, or even a frequent, feature of cases examined by the authors. There is, in fact, *no* typical or characteristic blood-picture in this disease—merely that of a consecutive, or what is usually called a "secondary," anæmia, and any variations found in certain patients are usually to be explained by the occurrence of some complication. Periods of quiescence, or even the spontaneous diminution in the size of the enlarged nodes, not infrequently occur, especially as a terminal phenomenon; but, although deep X-ray treatment has in some cases apparently been beneficial, especially if applied sufficiently early, the condition is, as a rule, progressive, and practically always leads to a fatal termination. Death may supervene from asthenia, or from pressure of the enlarged nodes upon important structures, such as the trachea or bronchi, lungs, heart, bile-duct, or some of the great vessels or nerves, resulting in dyspnœa, dropsy, obstructive jaundice, paralysis, and other phenomena. There appears to be little tendency to the occurrence of hæmorrhages.

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[1] Thomas Hodgkin : " On Some Morbid Appearances of the Absorbent Glands and Spleen." *Transactions of the Medico-Chirurgical Society of London,* 1832, **17**, 68–114.

[2] *Text-book of Pathology,* 5th ed., 1941, p. 508.

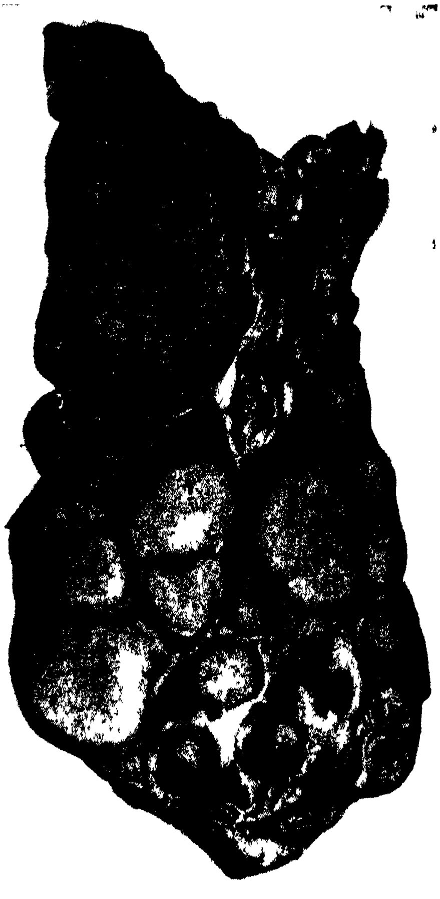
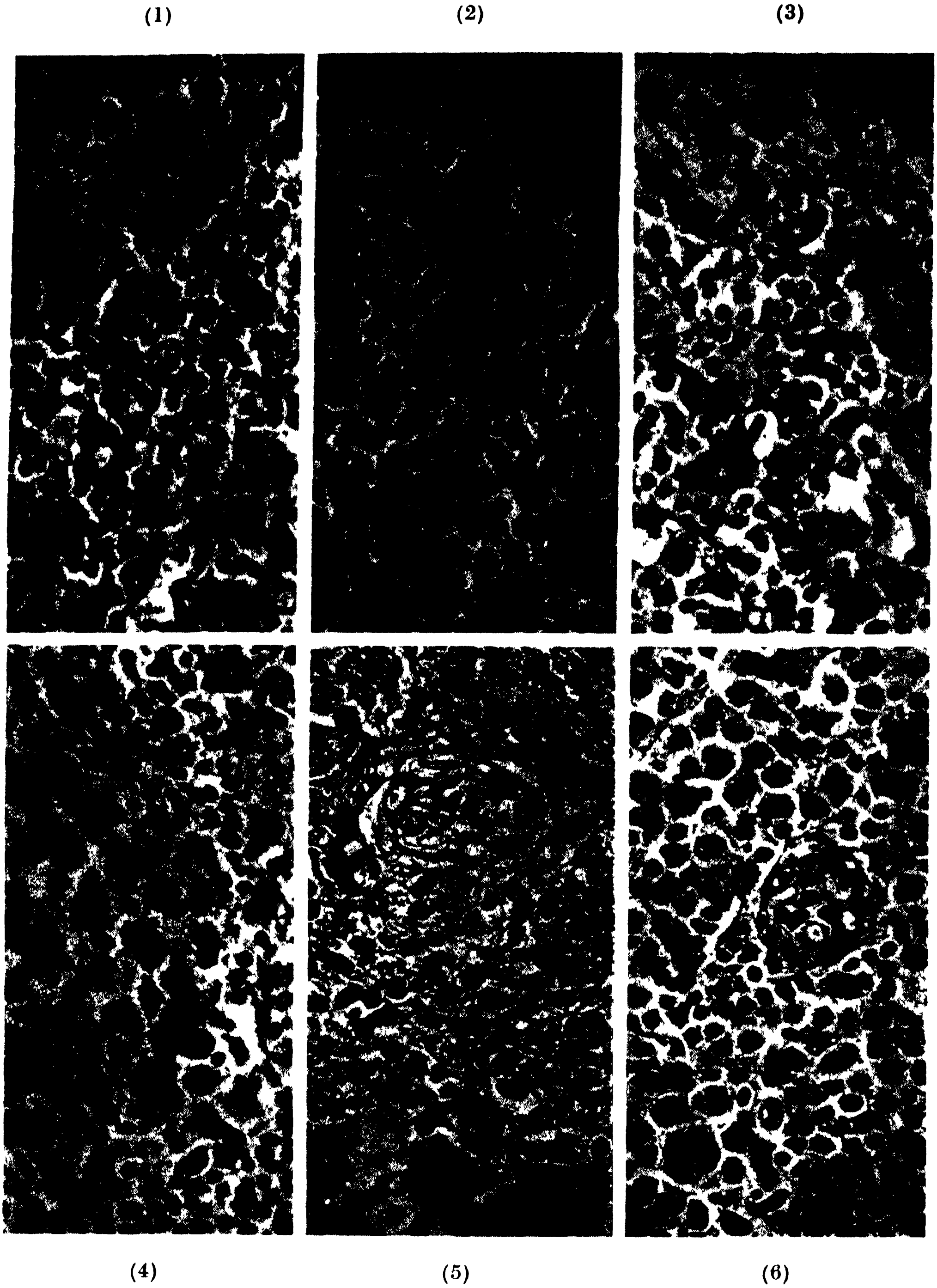


FIG. 376. Hodgkin's disease or lymphadenoma. Large tumour-like mass of lymph-nodes from axilla.

Ætiology. Practically nothing is known of the ultimate cause of the disease. Males are more commonly attacked than females, and it is during adolescence and early adult life that the majority of cases occur. Although the condition in some ways resembles tumour-formation, it has close analogies with certain of the chronic infective processes, especially tuberculosis and syphilis, and it appears not unlikely that it may yet be found to be caused by some analogous and as yet unknown infective agent. The disease is *not* due to the tubercle



Figs. 377–9. Lymphadenoma (Hodgkin's disease). Series of sections from several axillary lymph-nodes excised for diagnosis in an acute case in a male aged 35 : (1) early proliferation of lymphoid tissue, with only an occasional reticulo-endothelial cell. (2) Active proliferation of reticulo-endothelial cells, with several mitotic figures. In this and the remaining illustrations, there is progressive " crowding-out " of the lymphocytes by the proliferating reticulo-endothelial cells; and, from several of the latter, small giant-cells, *e.g.*, at the lower edge of (5) and (6), have developed ; whilst higher up in each of these figures there is also proliferation of perithelial cells around small vessels. (1, 2, 5 and 6 : Leishman's stain ; 3 and 4 : hæmatoxylin and eosin.) All × 400.

bacillus, as has been alleged by some observers, though tuberculosis is a not uncommon complication of the disease. In the past, observers have described the occurrence of "spirochætes," or the growth of "diphtheroid" and other organisms from the lymph-nodes or spleen in Hodgkin's disease, as possible ætiological factors. The evidence, however, of the relationship of such organisms to the disease is very inconclusive. In 1933, Mervyn Gordon claimed to have demonstrated the presence of a filtrable virus in lymphadenomatous tissue by producing a meningo-encephalitis in rabbits injected with the "virus." The reaction, however, does not appear to be specific, and Gordon's work in no way proves that the disease is of the nature of a virus-infection. At present, therefore, as we have stated, the ætiology of the disease must be regarded as still to be discovered.

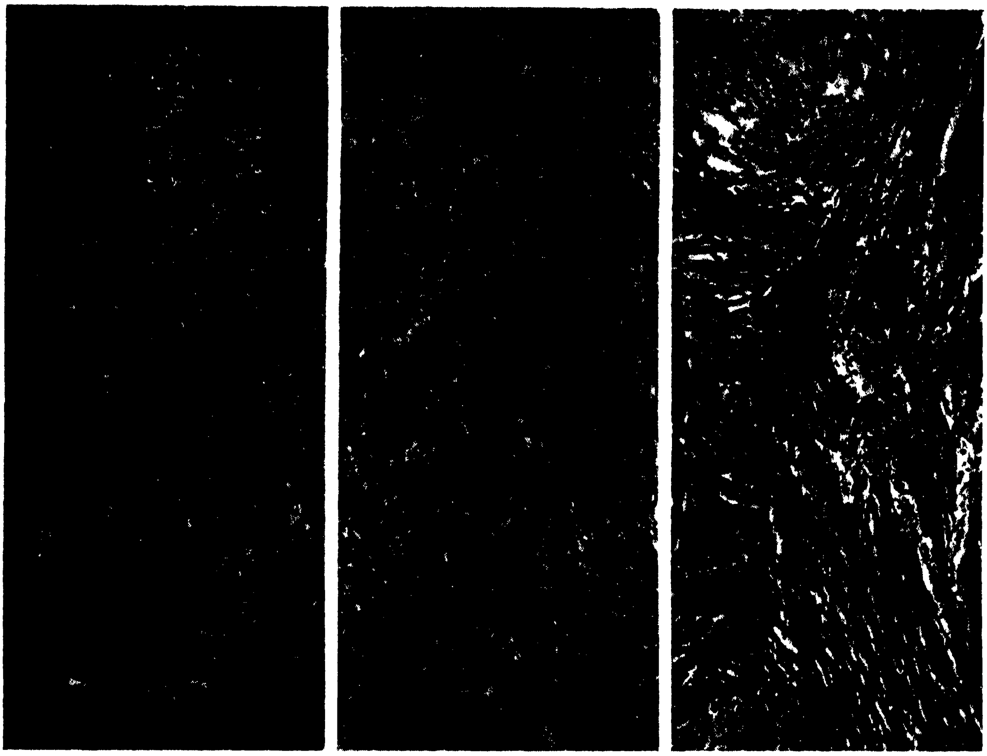
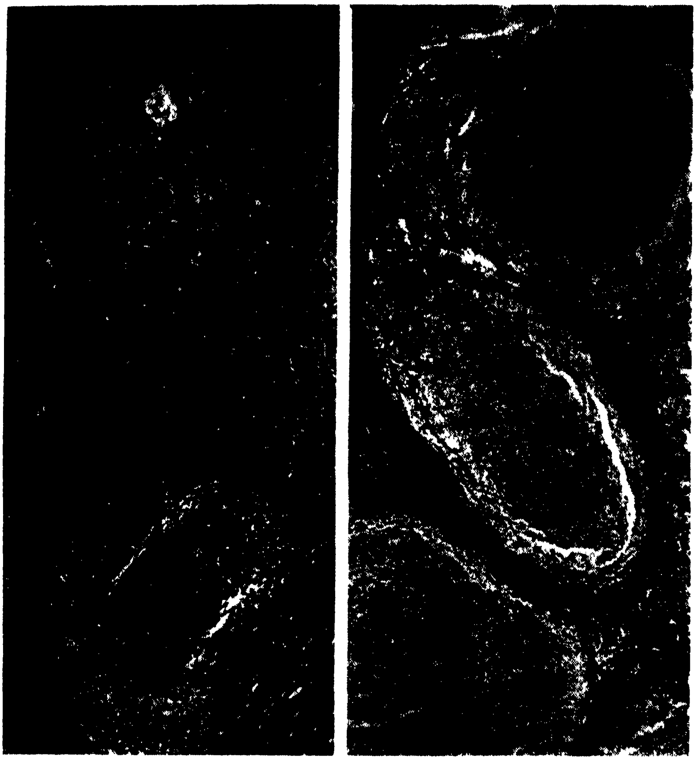

(1) (2) (3)

FIG. 380. Lymphadenoma (Hodgkin's disease). Low-power views of various lymph-nodes from the same case as the preceding *Figs.* 377–9. (1) Stained by Leishman's method for sections, showing the endothelial proliferation (the paler areas) amongst which are scattered eosinophil cells (the small darkly stained cells), together with commencing atrophy of the surrounding lymphoid tissue. (2) and (3), stained by Mallory's method for connective tissue, showing (2) the progressive fibrosis following upon the endothelial proliferation, with the cellular elements in process of disappearance, and (3) this progressive fibrosis becoming very pronounced. All × 100.

Morbid Anatomy. Though the disease may remain localised for a varying period to a single or to several groups of lymph-nodes—by the time death supervenes the nodes throughout the body, especially in the positions already mentioned, are usually greatly enlarged, and form considerable tumour-like masses, the individual nodes being often as large as a pigeon's or a hen's egg. Unless matted together by secondary inflammatory adhesions, they remain discrete, being held together by loose connective tissue which can be easily separated (Fig. 376, p. 677). There is usually no tendency for the process to infiltrate the surrounding parts, though such infiltration has been described in exceptional cases. Individual nodes vary in consistence. Typically, and particularly where the disease has lasted some time, they are indurated, firm, and elastic ; but, in acute cases, the nodes tend to be soft. It is, however, not uncommon to find softer and more indurated nodes side by side in the same case (*see* Figs. 377 to 381). On section, they show a pale pinkish tint, particularly in the acute cases, or commonly, as the disease becomes chronic, a semi-translucent greyish appearance, often with bands of an opaque yellowish colour running through them. Sometimes, the whole node exhibits this opaque yellowish appearance. Occasionally, small areas of caseation, simulating that of tuberculosis, are present, and microscopical examination may be necessary to distinguish between the two conditions. **Microscopically,** the earliest stage of the process is seen as a hyperplasia of the lymphoid tissue (No. 1 in Figs. 377–9), but proliferation of the reticulo-endothelial cells (*see* note on the "Reticuloses and Reticulo-Endothelioses" in Appendix, pp. 1262–4) rapidly supervenes and



(1) (2)

FIG. 381. Lymphadenoma (Hodgkin's disease). Two very low-power views to show an advanced degree of fibrosis in one of the axillary lymph-nodes from the same case, stained respectively by van Gieson's and by Mallory's methods for connective tissue. × 30.

a progressive increase of the reticulum itself leads eventually to fibrosis of the adenoid tissue and the gradual disappearance of the lymphoid cells (Figs. 380–1). Increase in the number of **eosinophil cells** in the earlier and more acute stages is of frequent occurrence, but a more constant and characteristic phenomenon, apart from the essential **proliferation of the reticulo-endothelial cells,** is the presence of **giant-cells,**[1] both mono- and multi-nucleated (Figs. 377–9), some of them analogous to those seen in syphilis and tuberculosis, and, like them, derived from endothelial and other similar " fixed cells." These giant-cells may have one or more spherical or ovoid nuclei, or sometimes (when seen in section) convoluted, horseshoe- or ring-shaped, and these have, on occasion, been mistaken for " basket-cells " or megakaryocytes like those of the bone-marrow. Still larger phagocytic multinucleated syncytial masses—best and most strikingly demonstrated in fresh-wet preparations (*cf.* various analogous cells illustrated in Plate XIII, opposite p. 380, Fig. 4 : and Plate XVII,

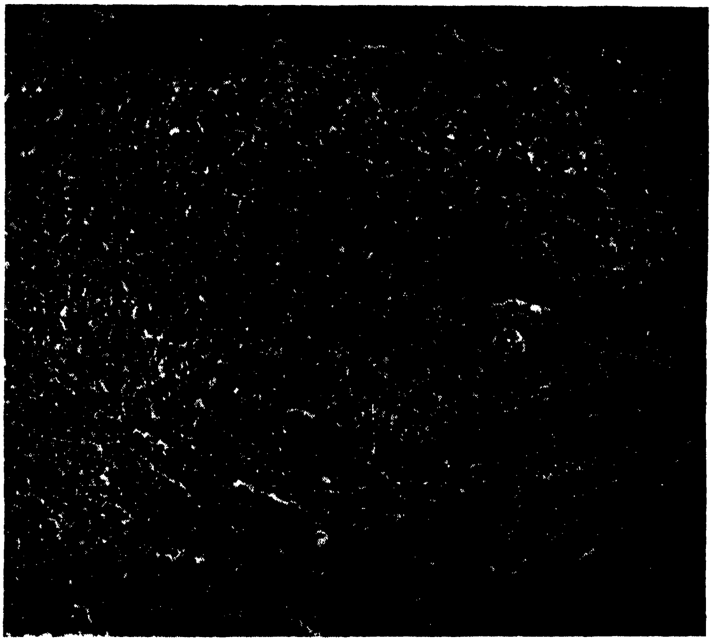


FIG. 382. Lymphadenoma (Hodgkin's disease). Section of spleen showing the lymphoid tissue of a Malpighian body undergoing compression-atrophy by the proliferated reticulo-endothelial cells, some of which have enlarged to form small giant-cells. Hæmatoxylin and eosin. × 100.

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[1] Certain of these giant-cells are sometimes referred to by writers as the " *cells of Sternberg,*" (of Vienna, 1898) or as " *Dorothy-Reed cells* " (*Johns Hopkins Hospital Reports,* 1902), but our old teacher, Professor W. S. Greenfield, had described them long previously, in his papers on " Specimens illustrative of the pathology of lymphadenoma and leucocythæmia " in the *Transactions of the Pathological Society of London,* 1878, **29**, 292 and elsewhere ; and we as his students were familiar with them from his lectures and demonstrations. A brief description of these giant-cells was given in our first edition, " Special Pathology," 1909, p. 135, in much the same terms as we have used in the above text of the present edition. In his paper in 1878, Professor Greenfield noted that, in the lymph-nodes " . . . there were a large number of multinucleated cells adherent to the trabeculæ, well seen on washing away the lymph cells. These multinucleated cells, containing four to eight or twelve nuclei, were often collected in clusters in the parts of the gland especially where the fibrous change was progressing."

opposite p. 616) rather than in sections—may also be found. In the later stages, the cellular elements are practically entirely replaced by collagenous fibrous tissue, and the structure comes to resemble that of dense scar-tissue (no. 3 in Fig. 380).

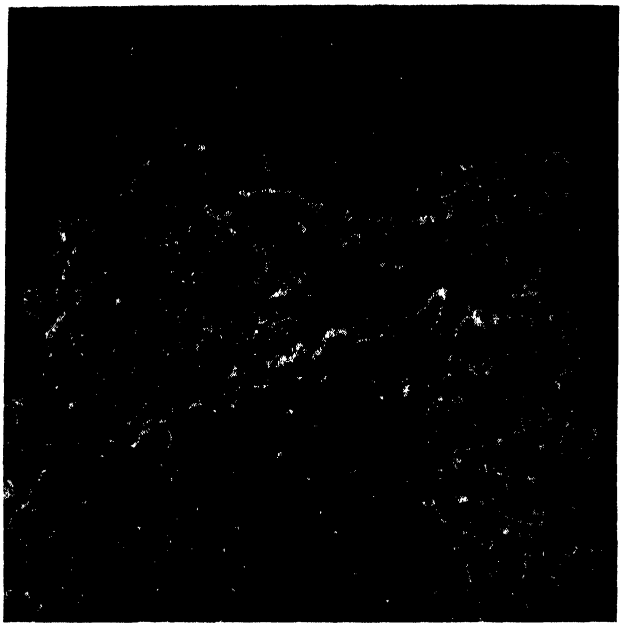

FIG. 383. Lymphadenoma (Hodgkin's disease). Section of liver showing a small nodule in a portal tract. Numerous giant-cells can be seen amongst the proliferating reticulo-endothelial cells. Hæmatoxylin and eosin. × 100.

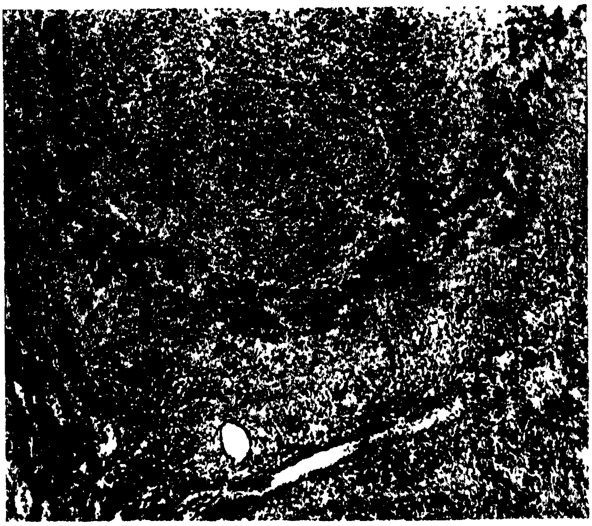

FIG. 384. Spleen in Hodgkin's disease. Malpighian body in process of fibrous obliteration, and surrounded by a ring of pigmented phagocytic cells. × 75.

Spleen (*see also* p. 695). The lesions of this organ are very variable. In some instances it is only slightly enlarged, whilst in others it may be moderately, or even greatly, increased in size. The natural shape is usually well preserved, and the organ firm in consistence. On section, to the naked eye, there may appear to be merely a congestive condition; but, again, there may be characteristic scattered whitish or yellowish-white, suet-like masses, which are usually distributed along the lines of the larger arteries. In the earlier and more acute cases, their colour is usually greyish-pink. These areas may be more or less diffuse, apparently spreading into the organ from the hilum along the lymphoid sheaths around the arteries. In other cases, they are more irregularly scattered and form isolated, rounded or irregularly-shaped masses, which may be as large as a bean or a cherry. They consist of altered peri-arterial lymphoid sheaths—*i.e.*, the Malpighian bodies and ellipoids—which have undergone a process similar to that already described as occurring in the lymph-nodes, namely (following, it may be, a preliminary and temporary hyperplasia of the lymphoid tissue proper), proliferation of the flattened endothelial cells and reticulum, and a corresponding diminution in the number of the contained lymphocytes. The process tends to spread into the surrounding areas of pulp, which thus become in part fibrosed. Where the process is spreading, the proliferated reticulo-endothelial cells, and giant-cells formed from these, are actively phagocytic towards red corpuscles, and usually contain large quantities of blood-pigment, producing around the periphery of the nodules a brownish zone (Fig. 384), which can often be distinguished with the naked eye.

The changes in the **bone-marrow** are somewhat variable, and may be of the nature of either a leucoblastic or an erythroblastic reaction. Characteristic lymphadenomatous nodules sometimes occur in the marrow, and show the same proliferation of the reticulum and fibrosis already described as occurring in the lymph-nodes and spleen.

Similar nodules are frequently found in the **liver** in such cases, usually associated with some degree of cirrhosis and fatty degeneration. These nodules occur in the connective tissue of the portal tracts as lymphoid areas (Fig. 383 opposite), which, later, undergo reticular proliferation, giant-cell formation, and then fibroid transformation. They are likewise occasionally seen in the kidneys, lungs, and even in the skin. The lymphoid tissue of the intestines—Peyer's patches and solitary follicles—and of the stomach may also become involved, and may, in rare instances, undergo ulceration.

GLANDULAR FEVER or INFECTIOUS MONONUCLEOSIS is an infective disease of unknown ætiology, which attacks both children and adults, and in which especially the cervical lymph-nodes, and often also the axillary and inguinal nodes, are enlarged. The mediastinal and abdominal nodes and the spleen may also be affected, as well as the lymphadenoid tissue of the throat, bronchi and intestine. Occasionally, the enlargement is less widespread, and may even, it is said, be restricted to a single cervical or other gland. Mild pyrexia is the rule, but sometimes the fever is considerable. Jaundice occurs in some cases, and is thought to be due either to an associated hepatitis or to pressure upon the bile-duct of enlarged lymph-nodes in the hilum of the organ. The blood usually shows a leucocytosis of up to 20,000 cells per c.mm.—sometimes more, especially in children. There is commonly a preliminary rise in the numbers of the polymorphonuclear leucocytes, followed and soon replaced by the characteristic increase of the mononuclears, both lymphocytes and monocytes, together with their parent-cells, *i.e.*, lymphoblasts and monoblasts. The findings in the blood often vary considerably within comparatively short intervals during the course of the illness, so that repeated blood-examinations may be required in order to be able to judge the general progress of the infection. One difficulty in making a speedy and accurate diagnosis is, in certain cases, to differentiate the blood-picture from that of lymphatic leukæmia ; and the Paul-Bunnell reaction (1932–33) to demonstrate in the patient's blood the presence of a heterophil antigen to sheep's red corpuscles is a useful aid to diagnosis. The introduction of this test was due to the accidental discovery that, in the blood of human patients suffering from infectious mononucleosis, there is developed, on and after about the fourth day of the illness, an antibody which agglutinates the washed red corpuscles of the sheep. This purely empiric reaction (though it is found also in certain cases of foreign-protein susceptibility, *e.g.*, in serum-sickness) is sufficiently constant to be useful as an aid to the differential diagnosis of infectious mononucleosis ; whilst, in those cases of the disease which resemble typhoid or paratyphoid fever, the specific agglutination-reactions of the serum against the causal organisms of these will be absent. Sternal bone-marrow puncture may also be usefully employed to differentiate the disease from lymphatic leukæmia, because, in infectious mononucleosis, the marrow does not show any appreciable lymphocytic infiltration such as supervenes in lymphatic leukæmia (pp. 632–3).

Microscopically, the enlarged lymph-nodes show hyperplasia of both their lymphoid and reticulo-endothelial cells. In some forms of the disease, which is protean in its characters, sore throat with ulceration and membrane-formation is present. This anginous form closely resembles Vincent's angina, the typical fusi-spirochætal organisms of which are often present. The specific causal agent of the disease itself is, however, as we have already stated, still unknown, although P. J. Wising (1939),[1] has succeeded in reproducing the disease by inoculating monkeys with an emulsion of the infected human lymph-nodes ; and also, during the course of his experiments, the disease was accidentally transmitted to man. It is not unlikely that the infection is due to a virus, but further investigation is still required to prove this assumption.

TUMOURS OF LYMPH-NODES and of LYMPHOID TISSUE generally. The classification of these presents many difficulties, as does also their differentiation from hyperplasias and other changes in certain of the so-called "blood-diseases," and from chronic inflammatory and infective enlargements (*see* pp. 1262–4). The following types of primary new growth may be distinguished.

Lymphoma. Tumours closely resembling proliferated lymphadenoid tissue, in which the lymphocytes, endothelial cells, and reticulum appear in practically their normal proportions, may occur. These are seen in the mediastinum, where they may arise from ordinary lymph-nodes, or occasionally from the thymus gland. Lymphomas may originate also in the tonsils, and in the cervical, abdominal, and other lymph-nodes. They have been described as occurring in the kidney, and in the lymph-nodes about the head of the pancreas and near the hilum of the liver. Some of these tumours are non-malignant, but, in other instances, there may be a tendency to the secondary spread to other lymph-nodes and lymphoid structures, *e.g.*, Peyer's patches or aggregated follicles, and the solitary lymphoid follicles of the intestine. These may ulcerate to form the so-called lymphomatous ulcers. Lymphomatous and lympho-sarcomatous tumours, and even some inflammatory hyperplasias of lymphoid tissue, may resemble one another so closely in their histological structure that it may be practically impossible, on microscopical evidence alone, to distinguish between them ; and, unless the clinical history of the case as a whole is considered in relation to the histological picture, it may be difficult in some cases to avoid mistakes in diagnosis.

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[1] *Acta medica scandinavica*, **1939, 98, 328.**

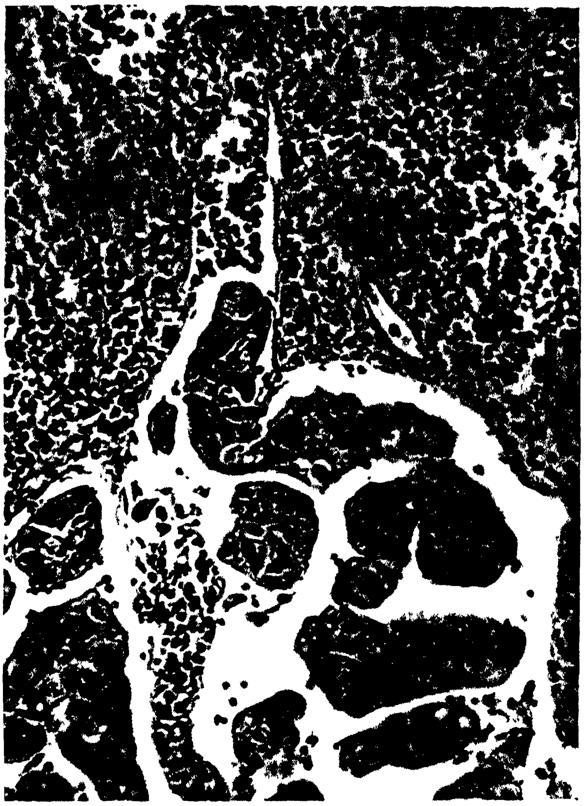

FIG. 385. Axillary lymph-node, showing secondary invasion with cells of scirrhous cancer of breast. Hæmatoxylin and eosin. × 200.

Lymphosarcoma. In this highly malignant form of tumour, there is enormous increase in the number of lymphocytes or lymphocyte-like cells, with no corresponding increase of endothelial plates and reticulum, both of which structures remain extremely scanty or may even be absent. Such tumours arise most frequently from mediastinal and retroperitoneal lymph-nodes, but they may originate also from lymphoid tissue around the intra-pulmonary bronchi, and elsewhere.

The condition bears certain resemblances to Hodgkin's disease on naked-eye examination, but there is, in lymphosarcoma, a tendency towards destruction of the capsules of affected nodes, with infiltration of surrounding structures by direct extension. Two types of growth occur: in the one, the proliferating cells represent lymphocytes or lymphoblasts, and in the other, the cells of the tumour are derived from the reticulo-endothelial cells of the lymphadenoid tissue (*see* p. 1262). The distinction is of importance, since the former type responds to therapeutic irradiation better than the latter variety. In connection with the question of the nature of some malignant growths in the mediastinum, it may be mentioned that **metastases** from certain types of **bronchial carcinoma,** *e.g.*, the so-called oat-celled variety (pp. 571 and 1151), have in the past not infrequently been mistaken for, and described as, "lymphosarcomatous" tumours, and sometimes even as "endotheliomas" of the pleura or lung.

Secondary growths of malignant epithelial tumours in nodes are extremely common, for example, implication of the cervical nodes in squamous epithelioma of the tongue: of the axillary and other groups in scirrhous and other malignant tumours of the mammary gland: or of the mesenteric and retroperitoneal nodes in gastro-intestinal cancers. Secondary invasion of the lymph-nodes by sarcomas is also by no means uncommon; but **malignant melanomas,** in the past often regarded as "a variety of sarcoma spreading especially by lymphatics," are now by most authorities believed to be **carcinomatous** (pp. 323–4).

LYMPHATISM, "STATUS LYMPHATICUS" or "THYMO-LYMPHATICUS"

Though comparatively rare, this condition is one of considerable importance, owing to the liability of those who are its victims—most commonly children or young adults—to sudden death from apparently trivial causes such as a fright or shock, *e.g.*, from immersion in cold water, or on the administration of an anæsthetic such as chloroform or ether. The presence of the condition has, in many such cases, been unsuspected during life, and may be revealed for the first time by post-mortem examination. There is general hyperplasia of the lymphoid tissue throughout the body. The lymph-nodes, especially those in the mediastinum and abdomen, are enlarged, as are also the tonsils and pharyngeal adenoid tissue, thymus, and spleen, and the Peyer's patches or aggregated follicles and other adenoid tissue in the intestine, the solitary follicles of the large intestine being specially prominent. The posterior portion of the dorsum of the tongue is often unusually rough, especially in the neighbourhood of and posterior to the circumvallate papillæ, which may be themselves distinctly hypertrophied (p. 704). The enlargement of the thymus (p. 839) is frequently considerable; and to pressure of it upon the trachea the fatal issue has in some cases of lymphatism been attributed. In the majority of cases, this is certainly not the true explanation, and some authorities now believe that some toxic substance is elaborated and poured into the system from the hyperplastic lymphoid tissues—the condition of so-called "lymphotoxæmia." The special Joint-Committee of the Medical Research Council and the Pathological Society of Great Britain and Ireland, in its report issued in 1931, stated that the data collected "afford no evidence that so-called 'status lymphaticus' has any existence as a pathological entity." In spite of this pronouncement, many workers with considerable experience of post-mortem examinations in cases of sudden death continue to ascribe death in certain instances to a condition of "lymphatism," in which the only abnormal post-mortem findings were a general hyperplasia of the lymphoid tissue throughout the body. The questions involved in this difference of opinion are by no means settled. Hyperplasia of the bone-marrow (fatty, being replaced by red, marrow), and of the thyroid gland, are recorded in some cases, as is also an under-development or hypoplasia of the heart and great vessels, and of the chromaphil tissues, especially the suprarenal medulla. This latter feature may be significant in connection with acute circulatory failure as a cause of sudden death in this case-group. Areas of "small-celled infiltration" and other inflammatory and degenerative changes have been described as occurring in the myocardium. The cause and exact nature of the condition must, therefore, be regarded as still unknown.

HÆMAL LYMPH-NODES

(Hæmolymph-Nodes)

These closely resemble ordinary lymph-nodes in structure, the chief point of difference being their reddish colour from the presence of blood in place of lymph in the sinus-systems between the lymphoid follicles. In some respects they present a structure analogous to that of the spleen, and have by some even been regarded as similar in nature to that organ. Little is yet known of their physiology and pathology, but enlargement of them has been observed in some "blood-diseases" such as Addisonian anæmia and splenic anæmia, and also in exophthalmic or toxic goitre (p. 823 *et seq.*) and Hodgkin's disease. The nodes are found especially in the abdomen, *e.g.*, about the brim of the pelvis, and along the aorta and inferior vena cava, iliacs and splenic vessels. Considerable phagocytic activity towards red blood-corpuscles on the part of the endothelial cells of the sinuses is usually to be observed in these nodes, especially in the diseases mentioned.

CHAPTER XX

DISEASES OF THE SPLEEN

Anatomy and Physiology:—

THE **spleen** is an organ which is not essential to life (*see under* Splenectomy p. 700) and all its functions are not yet fully understood. Beneath its peritoneal investment, the organ is covered by a thin, tough, fibro-elastic membrane, from the deep aspect of which dense **trabeculæ** composed of collagenous and elastic fibres, fibrous-tissue cells and smooth-muscle cells pass into the organ to form its supporting framework. The meshes of this framework are occupied by **lymphocytes** of various sizes in a **reticulo-endothelial stroma.** The blood is carried into the spleen by branches of the splenic artery which are distributed from the hilum within the trabeculæ, in and along with which they branch, becoming progressively smaller in calibre. In the trabeculæ are also the corresponding veins, returning the blood to the hilum, where some five or six of them emerge and unite to form the main splenic vein, which is peculiar in the large amount of muscular tissue in its outer as well as in its middle coat. The **arteries** passing inwards in the trabeculæ eventually separate from the veins, and, after they do so, the structure of their walls, which so far has corresponded with that of the medium-sized arteries, alters in character. The collagenous and elastic fibres of the outer wall become thinner and more loosely arranged and form a network in the meshes of which groups of lymphocytes are situated. When traced further along their course, a thick cylindrical **sheath of lymphoid tissue** is found surrounding and accompanying all the smaller branches almost to the capillaries. In many places along the course of these arterial branches, the sheaths form well-defined globular or ovoid thickenings of this lymphoid tissue—the splenic lymphatic nodules or Malpighian bodies. Throughout their course, the arteries give off branches to the trabeculæ and Malpighian bodies, and, after the disappearance of the lymphoid sheath, they end in capillaries which enter the splenic pulp. The trabecular veins associated with the arteries arise from an aggregation of small veins coming directly from the pulp. These veins have thin walls composed only of endothelial tissue, and receive blood from the **venous sinuses** which form a continuous communicating network throughout the pulp. These sinuses have a wide lumen, irregular in shape and varying in size according to the blood-content of the organ at any particular time. Many authors believe that, at certain points in their course, the capillaries open freely into the tissue-spaces of the pulp and not directly into the venous sinuses, and that the blood thus penetrates the tissue and is slowly filtered until it reaches the free beginnings of the venous channels. This " open " course is said to act intermittently as the result of muscular contraction of the organ. Other authors, whilst admitting the existence of this " open " course, maintain that part of the blood passes directly from the arterial system to the venous system, the capillaries opening directly into the venous sinuses.

In the " open " course, certain sections of the walls of the fine arterioles entering the pulp are devoid of muscular tissue, the place of which is taken by cells of endothelial type, and between those cells the blood enters the pulp. These " ellipsoids," as they are named, are contractile and act as valves, so that the blood can pass out of the vessels, but is unable to enter them from the pulp. Because of this arrangement of the vascular mechanism, the spleen is enabled to act as a " blood-filter."

The innervation of the spleen, and the control of its contractile tissue, *e.g.* in the capsule and trabeculæ, and in the blood-vessels, including the afferent and efferent sphincters of the sinuses, are important in the functioning of the organ, and for a detailed description of these we refer our readers to that given in Schafer's "Essentials of Histology," 14th edition, 1938, pp. 242–249, and Fig. 296, giving Carleton and Knisely's diagram and their interpretation of the splenic circulation, which will help to the understanding of the above description. They explain that the sinuses form a storage-system, the arterial blood passing through the Malpighian bodies and ellipsoids into the sinuses, which possess afferent and efferent sphincters controlling them : and that there is also a by-pass or "straight-through" capillary enabling blood to run from the arteriole after it has passed through Malpighian body and ellipsoid, into the radicles of the splenic vein *without* going through the storage-sinuses.

Of the **functions** of the spleen—which has been called the "portal heart"—its capacity for alternate contraction and relaxation is of importance, for by its **contraction** extra blood from its reserves, stored in the sinus-system of the pulp, can be added to the general circulation when required, as in cases of hæmorrhage, or where respiratory embarrassment calls for increased oxygen-carrying capacity in the blood.

Blood-formation, including erythropoiesis, is a function of the spleen in the fœtus ; but in extra-uterine life, except for the production of lymphocytes and large monocytes amongst the white-cell series, other varieties of hæmopoiesis, *e.g.* of red corpuscles and granular leucocytes, are seen only in certain pathological conditions, as, for example, possibly in von Jaksch's anæmia (pp. 661–2 and 698).

Blood-destruction. The spleen, along with the liver and bone-marrow, constitutes an important portion of the **reticulo-endothelial system** (*see* p. 1262), and it therefore plays a prominent part in the destruction of effete red corpuscles, and the breaking up of hæmoglobin, and is also concerned with the metabolism of **iron** and the production of **bile-pigment**—functions which are often greatly increased in many pathological conditions, notably in the anæmias. The spleen is also concerned with the destruction of blood-platelets (pp. 602 and 700–1).

The close association of the spleen with the liver, and especially its anatomical relations to the portal circulation, by which contraction of the spleen tends to aid blood-flow through the liver, accounts for the simultaneous involvement of the two organs in certain pathological conditions, notably in Banti's disease (p. 696 *et seq.*).

The influence of the spleen on **blood-coagulation** is not fully understood. Following splenectomy, an increase of blood-platelets is usual, but there is no definite evidence as to whether this is the result of a lessened destruction of the platelets by the spleen, or an increase in their production in the bone-marrow following withdrawal of influences exerted by the spleen—the former alternative being the more probable.

The **cholesterogenic function** of the spleen has been studied in connection with the metabolic disturbances associated with cells of the reticulo-endothelial system in Gaucher's disease (pp. 700 and 1071) and in hypercholesterolæmic splenomegaly. That this function is associated in some way with fat-metabolism appears certain, but the problem has not yet been investigated at all fully.

Immunity. The spleen probably is concerned in the production of antibodies and in other processes connected with immunity, but these problems also require much further investigation.

Malformations and Malpositions. Accessory spleens, usually small in size and therefore known as "spleniculi," are common. They generally vary from the size of a pea up to that of a cherry, and are more or less spherical in shape. As a rule, such spleniculi are few in number—commonly only one is found—and are situated usually near the hilum of the main organ. More rarely, they are multiple, and may be situated elsewhere, *e.g.*, in the mesentery. They almost always participate in any pathological enlargement and other abnormality of the main organ.

Thickening, patchy or general, of the peritoneal investment and capsule of the spleen is common. It may result from any of the usual causes of such conditions, including previous attacks of peritonitis or of chronic granulomatous diseases such as tubercle or syphilis. It may be localised over old infarcts or may arise from and over repeated **hæmorrhages** into the layers of the *capsule, giving rise to the peculiar patchy fibrosis sometimes referred to as* **"iced spleen."** *On incising such a patch, recent hæmorrhage may be found* in its deeper layers, thus affording an explanation of an otherwise puzzling condition.

Movable (or "wandering") spleen is a condition which may result when, from general visceroptosis, the usual supports of the spleen are weakened and the ligaments and vessels become stretched. It is of importance chiefly from the possibility of twisting of the pedicle and constriction of the contained vessels, which may lead to interference with its blood-supply, and perhaps to necrosis.

Injuries of the Spleen. Rupture of the normal spleen occurs very occasionally "idiopathically," *e.g.*, in the pregnant female; but is not uncommon in severe crushing injuries to the trunk. Rupture, however, is a commoner occurrence if the organ has been previously diseased, and especially if it is enlarged, *e.g.*, from malaria, when some comparatively slight accident may cause it. In crushing injuries, the spleen is usually forcibly bent upon itself, and is ruptured on its stretched outer or convex surface, an accident which leads to extensive and perhaps fatal hæmorrhage.

Atrophic Changes in the Spleen. Atrophy of the spleen supervenes normally as a senile change, the Malpighian bodies, in common with lymphoid tissues in other parts of the body, becoming progressively less active and undergoing atrophic changes with advancing age. The pulp also becomes diminished in bulk, mainly from atrophy of its cells; and the fibrous tissue, especially of the trabeculæ, is relatively increased in amount. The capsule of the organ becomes wrinkled, and the weight of the spleen may fall as low as 2 or 2½ ozs. (60–75 grammes—its normal weight in the adult being 5½ to 7 ozs. or 150 to 200 grammes). On section, the tissue has a dull brownish-red colour, the Malpighian bodies being inconspicuous, and the trabeculæ showing as pale, ragged, fibrous threads, standing out above the general level of the cut surface. The consistence of the atrophied organ varies, but, most frequently, it is tough, dry, and soft, rather resembling a piece of flabby muscle to the touch.

The majority of pathological changes in the spleen are, however, associated with **enlargement** of the organ.

Amyloid Degeneration. This degeneration affects the Malpighian bodies, producing "**sago-amyloid disease**" of the spleen: or the reticulum of the pulp and the walls of the venous sinuses, constituting the "**diffuse form**"; but in most instances there is a combination of both types, though in varying relative degrees of each (pp. 210–212 and Fig. 103, and Plate X, opposite p. 210, Figs. 1 and 2).

The sago-amyloid type is much the commoner of the two. The spleen is usually moderately enlarged, perhaps to twice its normal bulk, but, in many cases, there may be little increase, and even some diminution, in size. In consistence it is firm, its cut margins remaining sharp, and its natural shape maintained. The cut surface of the organ is seen to be studded with small, rounded, translucent areas about the size of a pin's head or slightly larger. On the application of iodine, these areas become stained a deep mahogany-brown colour (*cf.* Plate X, opposite p. 210, Fig. 1 and Fig. 103, p. 211). The intervening pulp-tissue is usually of a dark-red colour from chronic venous congestion.

The diffuse form is associated more especially with syphilis—though it may be found also in chronic tuberculosis—and in it there is, as noted above, an extensive affection of the reticulum of the splenic pulp and the walls of the venous sinuses. The enlargement of the organ is usually rather more pronounced than in the sago-amyloid type, the spleen being very firm and resembling india-rubber in consistence. The cut surface has a more or less homogeneous, semi-translucent appearance, often with a pale pinkish-red tint. The Malpighian bodies are widely separated and minute, and may be almost, or even quite, invisible to the naked eye. With iodine, a uniform deep mahogany-brown coloration is obtained (Fig. 103, p. 211). The microscopical appearances of the organ when affected with amyloid degeneration are described on p. 210.

Hyaline Degeneration. This occurs especially in acute infective diseases such as typhoid, scarlet fever and diphtheria. A description of the condition is given on p. 214.

Pigmentation and Phagocytosis in the Spleen. Owing to the hæmolytic activities of the spleen, the presence of a certain amount of blood-derived pigment is a normal phenomenon, most of the pigment being contained within the phagocytic reticulo-endothelial cells of the pulp. In any condition characterised by increased blood-destruction, notably in the anæmias, in acute and chronic septicæmias and toxæmias, and especially in malaria, both acute and chronic (p. 382), the hæmolytic activities of the spleen, like those of the liver and bone-marrow, are increased, and, consequently, the phagocytic cells and their contained pigment are in greater evidence (*cf.* Plate XI, opposite p. 222, Fig. 2 : and Plate XVII, opposite p. 616, Figs. 2 and 6). Examples of such increased hæmolysis are to be seen in the spleen in untreated Addisonian or "pernicious" anæmia, the toxæmia of diphtheria, or in chronic malaria, though marked degrees of the change may be found in almost any analogous condition. The most pronounced degree of hæmosiderosis of the spleen is seen after repeated blood-transfusions. Apparently a proportionately larger share of the blood-pigment is taken up by phagocytes in the spleen under these conditions than when the patient's own red corpuscles alone are the source. The naked-eye evidence of such hæmolysis is seen as a distinct brownish tint of the splenic pulp. The pigment, when it contains iron, *e.g.*, in the case of untreated Addisonian anæmia, gives, in most cases, a Prussian-blue reaction if the organ is treated with solutions of potassium ferrocyanide and hydrochloric acid, but, in some instances, the reaction is not definite, probably on account of the iron being in somewhat firm union with organic material, the colour being a variable greenish-or bluish-black.

Post-mortem discoloration or pseudomelanosis (pp. 236–7)—generally of a dark greenish- or violet-black tint—is very common, especially on the lower part of the organ where it is in contact with the intestine. Such post-mortem discoloration is due to the action of sulphuretted hydrogen upon the iron of the blood or blood-pigment. It may be localised to the surface, or may penetrate the substance of the organ for a varying distance.

VASCULAR DERANGEMENTS OF THE SPLEEN :—

(*a*) **Acute or active hyperæmia** is discussed when dealing with the Spleen in Acute Diseases (p. 693, opposite).

(*b*) **Chronic Passive (Venous) Congestion.** This condition may form part of a general venous engorgement, as in diseases of the heart or lungs, in which the return of venous blood into the heart is impeded ; or it may be produced by obstruction of the portal circulation by disease of the liver, or from tumours or other lesions producing pressure on the portal or splenic veins. In the first type of case, the organ is usually moderately enlarged, and is firm in consistence. It becomes relatively thicker, and especially broader, in proportion to its length, often coming to have a somewhat oblong shape. The notches are generally well preserved (Fig. 73, p. 153). The capsule and trabeculæ are thickened, and the muscular fibres in them may be increased. In the most pronounced examples of the condition, seen in old-standing chronic mitral disease, the spleen may become so curved and rounded that the upper and lower poles approach the hilum and the organ then becomes known as " a cricket-ball spleen." The pulp has a characteristic dark purple-red colour, and the Malpighian bodies are so small and widely separated that they are indistinct and may be invisible on naked-eye examination, owing to compression by the engorged and dilated venous sinuses of the pulp. The large and medium-sized veins, which can be seen running in the trabeculæ, are dilated. On microscopical section, the widespread dilatation of the venous sinuses and veins can be well seen, and is associated with thickening of the trabeculæ and walls of the veins. The pulp is occupied mostly by the dilated venous sinuses, the walls of which, lined by endothelium, are abnormally distinct (Plate X, opposite p. 210, Fig. 2, in which, however, amyloid degeneration is also represented). The intervening pulp-tissue, and also the Malpighian bodies, are atrophied from pressure. There is, usually, a considerable amount of blood-pigment within the phagocytic reticulo-endothelial cells, and, to a less extent, free in the meshes of the pulp. Chronic venous congestion, resulting from obstruction to the portal or splenic veins, gives rise to a condition of the spleen similar to that just described, except that the change is usually brought about more quickly and the organ is less firm and does not assume the rounded or " the cricket-ball " form.

(*c*) **Infarction of the Spleen.** The subject of infarction in general is discussed on p. 167 *et seq.* Infarcts are common in the spleen (p. 175), and may be due to embolism, *e.g.*, in septic endocarditis : or to thrombosis, which is the probable cause of the infarcts in cases of myelogenous leukæmia (p. 629), splenic anæmia (p. 696), and analogous diseases. Thrombosis of the main splenic vein produces a condition of infarction of the whole organ, but is uncommon.

Infarcts in the spleen may be multiple, and are often of considerable size. They are observed most frequently on the convex outer surface or borders of the spleen, though, when large, they may occupy a horizontal or transverse zone through the entire thickness of the organ. Seen on the outer surface, they may be irregularly rounded, or may form a bar-like area running across the spleen (Fig. 86, p. 175). In the former case, they are usually irregularly wedge-shaped on section, with the base of the wedge towards the free surface. In infarction, the whole spleen may be considerably enlarged, especially where the infarcts are multiple from repeated embolism. Infarcts of the spleen, unless of small size, are usually, but not invariably, non-hæmorrhagic, but they always show a hæmorrhagic border. Soon they become pale, with an active zone of congestion in the living tissue surrounding the infarcted area, and "inflammatory" cells migrate in large numbers into the dead tissues of the infarct. Gradual organisation follows, and the infarct shrinks in size, partly as a result of this, and partly from absorption following autolysis of the dead tissues. Finally, definite fibrosis sets in and the contraction of the fibrous tissue results in further shrinkage of the old area of infarction which may ultimately be reduced to a mere fibrous scar, or narrow wedge-shaped area of firm fibrous tissue, depressed below the surface (Fig. 87, p. 176). A local peritonitic reaction sometimes occurs over the area of infarction, and adhesions result. Where the causal emboli are septic, as in septic endocarditis (p. 455), or where secondary infection with pyogenic organisms occurs, the infarcts are liable to become softened, and break down to form abscesses, which may burst and produce general peritonitis or, if localised by adhesions, give rise to the condition of peri-splenic abscess.

THE SPLEEN IN ACUTE TOXIC AND SEPTIC DISEASES. In most **acute infective fevers, acute congestion** of the spleen occurs, and is regarded as a reaction or attempt to antagonise the toxins or other bacterial products or to destroy the causal organisms themselves. The increase in size is due partly to congestion of the pulp and swelling of the Malpighian bodies; but, later, it results more especially from the proliferation of reticulo-endothelial and pulp-cells, and the accumulation of leucocytes in the tissues of the organ. The naked-eye appearance of the enlarged spleen varies considerably, however, according to the nature of the causal organism or infective agent, and two differing types may be seen. In **typhus fever,** the spleen is enlarged, soft and pale pinkish-white. In **typhoid,** it is more usually a deep red and may attain a considerable size, an important diagnostic point when taken along with the characteristic leucopenia, and "rose-spots" if present—confirmed by culture of the bacillus itself from the blood or bone-marrow (pp. 606 and 751–2): and, later, by the development of the specific agglutination-reaction in the patient's serum against the bacillus (pp. 130–1). Clumps of *Bacterium typhosum* are often found in the spleen-pulp after death, and their presence may be demonstrable both culturally and microscopically. If the bacilli are scanty, the spleen can be incubated over-night, and, as the result of such artificial "culture" within the organ itself, they are then often found in greatly increased numbers. On post-mortem examination, the typhoid spleen is usually fairly firm—not softened—and the Malpighian bodies, in individual cases, may or may not be enlarged—the most important change in the organ being the pronounced proliferation of the reticulo-endothelial cells of the pulp. In **erysipelas** and other **streptococcal** infections, in **pneumonia,** and in **staphylococcal** cases, the spleen is often pale, the diffluent pulp having a greyish-pink tint, though the occurrence of hæmorrhage may produce a coloration which is distinctly red. In these latter cases, the spleen is so extremely soft that it is very easily ruptured on removing it from the body;

and, on section, the pulp can be readily scraped or washed away. In some cases, *e.g.*, in **scarlet fever,** the Malpighian bodies, as well as the pulp-tissue, may be considerably swollen.

Apparently the only fever in which no enlargement of the spleen has been demonstrated, even on post-mortem examination, is yellow fever, perhaps on account of the amount of blood lost by gastric hæmorrhage.

In many bacterial diseases in addition to typhoid (p. 693), *e.g.*, in **Mediterranean (Malta) fever,** or **staphylococcal** and **streptococcal septicæmias,** the causal organisms may be found specially aggregated in the spleen, and may be demonstrated on microscopical or cultural examination. In subacute bacterial endocarditis and in septicæmias of milder character, the enlargement of the spleen is often considerable and its substance pinkish in colour and not diffluent. Similar appearances occur in undulant and relapsing fevers.

Actual suppuration in the spleen, apart from its occurrence in ulcerative endocarditis and pyæmia, is exceedingly uncommon. Secondary abscesses may occur, though rarely, in typhoid fever. Such abscesses in the spleen tend to occur towards the surface, where they may rupture and, if localised by adhesions, give rise to perisplenic abscess.

TUBERCULOSIS OF THE SPLEEN. Tuberculous infection of the spleen is always secondary. The surface of the organ may be involved in tuberculous peritonitis, and tuberculous adhesions of the spleen to the surrounding organs and tissues, especially the diaphragm, are common. In generalised acute miliary tuberculosis, numerous small, greyish-white, opaque, nodular areas are found scattered throughout the substance of the organ and under the capsule. They can be distinguished from the Malpighian bodies, which they otherwise resemble, by being somewhat firmer and more prominent, and by being found on the surface of the organ as well as in the pulp. On microscopical examination, they may occur in any part of the splenic tissue, they are found most frequently along the course of the arteries, and are especially numerous in the Malpighian bodies. Typical tuberculous giant-cells are often present, but proliferative changes are, as a general rule, not a prominent feature.

In the less common chronic type, the yellowish-white caseous nodules, sometimes a third or a quarter of an inch in diameter (Fig. 43, p. 76), are seen especially in children. The nodules vary in consistence, but are often soft and easily washed out, leaving a series of holes on the cut surface. A similar caseous condition is found in the liver and kidneys of these cases. Larger tuberculous nodules, the so-called "tuberculomata," sometimes the size of or even larger than a walnut, are found occasionally in the spleens of children, especially in cases of tabes mesenterica (p. 69).

LEPROSY. In leprosy, and especially in advanced cases, the proliferated and enlarged reticulo-endothelial cells of the spleen-pulp contain great numbers of the causal organism, *Bacillus* (or *Mycobacterium*) *lepræ* (p. 79).

SYPHILIS does not often produce any naked-eye lesions in the spleen sufficiently characteristic to be of much diagnostic value, though the organ may be enlarged in the congenital form, especially where still-birth has resulted, and in the more acute febrile forms of the disease. There is usually definite, and sometimes extreme, proliferation of the endothelial cells lining the pulp-sinuses. Gummata may occur, but are uncommon (Fig. 46, p. 82). Deep, irregular cicatrices, sending fibrous bands into the interior of the organ, may result from the absorption of these—*cf.* the similar phenomena seen in the liver (pp. 85–6). *Treponema pallidum* may be present in large, and often in enormous, numbers in the splenic lesions, especially in congenital syphilis in infants and young children. The relationship of syphilis to amyloid disease is discussed on p. 209.

LYMPHADENOMA, HODGKIN'S DISEASE or PRIMARY FIBRO-MYELOID MEDULLARY RETICULOSIS (*see also* pp. 123, 676 and 1262–4). In this disease, the spleen, in common with the rest of the reticulo-endothelial tissues of the body, is always involved as the disease becomes generalised. According to the stage of the disease and the course run in any individual case, one of three types of splenic change may be found. In some cases, there is merely a general enlargement due to congestion and increase of the pulp-reticulum, without any definite naked-eye, or even microscopical, lesions in the Malpighian bodies, though diffuse cellular changes may be present in the pulp. In the second type, the characteristic changes in the Malpighian bodies, described on p. 683, are present either in patches or throughout the whole organ. In the third type, the granulomatous and fibrous masses may be so large that, as they lie embedded in the surrounding congested splenic pulp, they have the appearance of irregular or even angular lumps in a cold suet-pudding or sausage.

TUMOURS OF THE SPLEEN. Primary tumours of the spleen are exceptionally rare. Lymphomas, lymphosarcomas, and endotheliomas have been described. Secondary growths of carcinoma and sarcoma, and especially of malignant melanoma (p. 324), *may* occur, but, except where its surface is involved as part of a general peritoneal spread, the spleen, as a rule, escapes the presence of metastases, even when these are numerous in other organs (p. 273). This may be due to the active phagocytic processes and ferment-reactions which constitute a large part of the function of the organ.

ANIMAL PARASITES. Hydatid-cysts may occur in the spleen, but are not common. They may be of large size, and are usually associated with the presence of similar cysts in the liver (p. 401). Cysts due to *Cysticerci* and to *Pentastoma denticulatum* have also been found. The spleen may be enlarged in various forms of schistosomiasis (" Egyptian splenomegaly," pp. 392, 698 and 700).

Malarial (p. 382) **and other protozoal parasites,** *e.g.*, the **Leishman-Donovan bodies of Kala-Azar** (p. 370), may pass certain stages of their life-cycles in the spleen, as well as in the bone-marrow and elsewhere. Reference has already been made on p. 382 to the acute enlargement of the organ during a paroxysm of malaria : whilst a chronic enlargement may be the result of a series of such acute attacks. In the latter case, the enlargement may be very considerable, and the enlarged organ (" ague-cake ") is liable to rupture from injury. There may be thickening of the capsule from the occurrence of perisplenitis. The trabeculæ and adenoid reticulum become coarser ; and the condition is usually associated with chronic venous congestion. The Malpighian bodies tend to become atrophied ; and the most characteristic phenomenon is the proliferation, enlargement and phagocytic activity of the endothelial cells, which may contain numerous infested red corpuscles and parasites, and the pigment derived from these.

SPLENIC ENLARGEMENTS[1]

In certain diseases, disorders or syndromes, affecting the bone-marrow, circulating blood, and spleen, and perhaps the liver, and in some cases the lymph-nodes, the spleen itself is sometimes considerably, and occasionally greatly or even enormously, enlarged.

SPLENIC ANÆMIA or HEPATO-LIENAL FIBROSIS. This very chronic disease or group of diseases—" syndrome " would perhaps in most instances be the most appropriate term—is characterised by great enlargement of the spleen and the development of a gradually increasing, and, towards its termination, a profound, degree of anæmia. The disorder attacks young adults especially, and is commoner in males than in females ; and it is now generally agreed that the main clinical characteristic is **progressive anæmia,** associated with a varying degree of **fibrosis** of both **liver** and **spleen—hepato-lienal fibrosis.** During the earlier phases of the disorder, which may last for many years, the spleen undergoes progressive enlargement, with gradually increasing weakness of the patient, digestive disturbances, and, at first, a moderate degree of anæmia. Later, the digestive disturbances—attacks of dyspepsia and diarrhœa —are associated with progressive anæmia : slight or moderate increase in the size of the liver, with an excess of urobilinogen (and, consequently, of its derivative urobilin) in the urine ; and, in some instances, especially in those described as examples of " **Banti's disease** " or " **Banti's syndrome,**" with cirrhosis of the liver and its accompaniments, ascites and jaundice, though in the earlier stages definite clinical evidence of this cirrhosis of the liver is often not elicited. The enlargement of the spleen[2] is associated, particularly in the

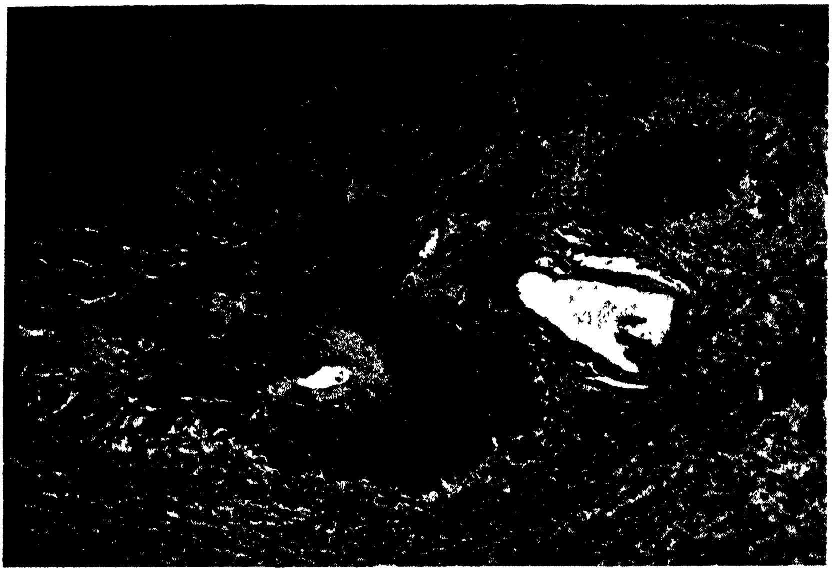

FIG. 386. *Siderotic nodule* in an enlarged spleen from a case of splenic anæmia in a male aged 26. (Ferrocyanide method for iron.) × 65.

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[1] See important note on the " Reticuloses and Reticulo-Endothelioses " on pp. 1262–4 at end of book.

[2] In McMichael's series of enlarged spleens (see footnote, p. 697, opposite), the average weight was between 800 and 900 grammes (1¾ to 2 lb.), with a maximum of 2,700 grammes (6 lb.).

later stages of the disease, with extreme diminution in the numbers of all the formed elements of the blood, including the platelets, and, usually, with the occurrence of hæmatemesis and melæna or, less frequently, of epistaxis and other forms of hæmorrhage. The spleen is firm in consistence, and has on section a homogeneous pinkish-red colour. Numerous hæmorrhages occur round the arterioles of the Malpighian bodies and ellipsoids ; and, because of the progressive pathological changes taking place in the intervening pulp, the Malpighian bodies are widely separated, compressed and atrophied, with proliferation and greatly increased phagocytic activity of the reticulo-endothelial cells, which ingest red corpuscles and consequently come to contain a large amount of blood-pigment. Sometimes the pigmentation assumes the form of "siderotic nodules" (Fig. 386), small patches of yellow-brown colour gradually replacing these hæmorrhagic areas, but often still surrounded by a zone of hæmorrhage. These areas of constantly recurring perivascular hæmorrhage gradually and progressively undergo organisation, and thus periarterial fibrosis and all transitions from recent hæmorrhage to fully fibrosed siderotic nodules are found. The latter contain hæmosiderin, phosphate of iron and calcium salts ; and the development of giant-cells in them is common. The venous sinuses are dilated, and their walls, in common with those of the arteries, arterioles and veins, show thickening, often associated with irregular dilatation and atheroma of the main splenic artery and thickening of the splenic and portal veins, in any of which vessels thrombosis is liable to supervene. In this way, owing to these changes and to the thickening of the adenoid reticulum and fibrous trabeculæ, there is produced the progressive fibrosis of all the tissues of the spleen characteristic of the enlargement of the organ in "splenic anæmia." Larger hæmorrhages, infarcts, and chronic perisplenitis, often with adhesions to neighbouring structures, are also common.

Opinion as to the efficacy of splenectomy (p. 700) as a cure for the disorder varies greatly, though some writers believe that, if the disease is not too advanced, excision of the organ, or in some cases ligature of the splenic artery, may "cure," or at all events alleviate, the condition.

Very divergent views have been expressed with regard to the causation and nature of "splenic anæmia." The vascular lesions in the organ, the hæmorrhages into its substance, and also from the stomach and intestine, have suggested that these may, in part at all events, be caused by an increase in blood-pressure in the portal circulation, which McMichael [1] regards as brought about by some preceding condition of **hepatitis,** although this need not necessarily be manifest as a definite cirrhotic change until later in the course of the disease. McNee [2] also believes that the periarterial hæmorrhages into the ellipsoids and the siderotic nodules to which they give rise are the result of backward pressure—the portal congestion leading to rupture of the arterioles at this particular part of their course because of their valve-like openings into the sinuses of the pulp.

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[1] J. McMichael, "The Pathology of Hepatolienal Fibrosis" (M. D. Thesis, Edinburgh University), *Jour. Path. and Bact.*, 1934, **39,** 481. In this and in a later paper in the *Edin. Med. Jour.*, 1935, **42,** 97, he analyses 96 cases of splenomegaly, diagnosed clinically as "splenic anæmia," 62 of which he regarded as examples of hepato-lienal fibrosis, with which he believes Banti's disease to be identical. One set of these cases included those in which cirrhosis of the liver was accompanied by splenomegaly : the second those in which, although obvious cirrhosis of the liver was still absent, the lesions in the spleen were of the same type as in Banti's disease, there being, in his opinion, no hard and fast dividing line between the two.

[2] J. W. McNee, in a series of papers, *e.g.*, in *Glasgow Med. Jour.*, 1929, **111,** 65, 193 and 288, and *Brit. Med. Jour.*, 1932, i, 1017, 1068 and 1111.

Instances of splenomegaly diagnosed as "splenic anæmia" in which cirrhosis of the liver has definitely developed, have sometimes been regarded as constituting a separate group or pathological entity—"Banti's disease"—but this is an ill-defined condition, and most observers now prefer to include cases of "**splenic anæmia**" and **Banti's disease,** as well as cases of so-called **Egyptian splenomegaly** (pp. 392 and 695), under the above general term of **hepato-lienal fibrosis,** a course which, until more is known as to their ultimate causation, has much to recommend it.

On the other hand, the great enlargement of the spleen, the progressive fibrosis, the pronounced anæmia and the alterations in the liver—opinion differs as to whether the hepatic lesions precede or follow those in the spleen—have suggested to some writers the possible presence and action of **an unknown toxic agent** at work in both of these organs, as well as in the bone-marrow, and which may exercise an inhibiting influence upon blood-formation. Another widely-held view is that the main phenomena of the disorder are brought about by the **abnormally increased capacity of the spleen for blood-destruction,** this possibility constituting the main argument for the employment of splenectomy (p. 700) in the treatment of appropriate cases.

PSEUDOLEUKÆMIA INFANTUM (Anæmia of von Jaksch). This disorder of infancy and early childhood is described on pp. 661–2, under Diseases of the Blood. It is a syndrome characterised by great enlargement of the spleen, and moderate increase in the size of the liver. Although the leucocytes in the blood are increased in numbers, there is no leukæmic infiltration of the liver or other organs and tissues. The lymphatic nodes may be slightly enlarged, and the bone-marrow is described as showing an erythroblastic reaction.

ERYTHROBLASTIC ANÆMIA of CHILDREN, sometimes called **Cooley's Anæmia** (p. 662). This disorder of infancy and childhood affects certain of the Mediterranean races, has a familial incidence, and in its blood-picture resembles von Jaksch's anæmia. The red corpuscles show great irregularity in size and shape, and are reduced usually to from 4,000,000 to 2,000,000 per c.mm., and the hæmoglobin to from 60 to 30 per cent. **Erythroblasts** of comparatively primitive type are present in the peripheral blood in large numbers, a phenomenon which is aggravated by splenectomy ; reticulocytes are numerous : and the white cells may reach 25,000 or in some cases even 50,000 per c.mm. Accumulations of hæmosiderin are found in the spleen, bone-marrow, liver, pancreas and stomach-wall. There is pronounced enlargement of the spleen, and the bone-marrow is hyperplastic and of immature type, and is present in excessive amount in many of the bones and especially in the enlarged spaces of the diploë, with thickening of the cranial and facial bones.

LEUKÆMIA (p. 625). The spleen is enlarged in varying degree in this group of disorders, such enlargement being most pronounced in the chronic forms, in which the spleen may be so large as to extend across the abdomen and reach the right iliac fossa. In **myelogenous leukæmia** (myelosis), the spleen (p. 629) is pink or pinkish-red in colour and infarcts are of common occurrence. Perisplenitis is always present to some degree and becomes especially pronounced when X-rays or radium have been used in treatment. Microscopically, there is disappearance of lymphoid tissue and the general picture closely resembles that of bone-marrow, the tissues of the organ being crowded with myeloid cells. In **lymphatic leukæmia,** the spleen (p. 633) tends to show less pronounced enlargement than in the myelogenous form, and microscopically there is hyperplasia of the lymphoid follicles and general increase of lymphocytes in the splenic pulp.

ACHOLURIC JAUNDICE (Acholuric Family Jaundice, Hæmolytic Icterus or Congenital Hæmolytic Anæmia) is a condition associated with a hereditary increased fragility and peculiar globular shape of the red blood-corpuscles (pp. 586–7 and 656–9). The spleen is enlarged, sometimes very considerably, and much iron-pigment is present, both in the endothelial cells and in the cells of the splenic pulp as the result of their greatly increased activity in the destruction of the abnormally globular red corpuscles. Splenectomy (p. 700) is often performed for this condition. Clinical improvement may supervene, but no effect is produced on the increased fragility of the red blood corpuscles, though the other changes leading to the jaundice disappear (p. 659).

POLYCYTHÆMIA. In the group of conditions (p. 638) included in this general term (polycythæmia rubra, polycythæmia vera, Vaquez-Osler disease and erythræmia), the seat of the primary disease is probably the bone-marrow, the phenomena in the spleen, *i.e.*, phagocytosis, increase of pigment, etc., being mainly those due to excessive hæmolytic activity. The degree of enlargement of the organ varies very much in different cases and also from time to time in individual instances of the disease. Microscopically, the splenic pulp is seen to be packed with enormous numbers of red blood-corpuscles, as though these had become filtered out from the overloaded circulating blood. No evidence of blood-formation within the spleen itself is to be observed.

THROMBOCYTOPENIC AND OTHER PURPURAS (p. 669). Whilst, in some cases, there are no demonstrable alterations in the spleen beyond slight enlargement, in others there occur changes similar to those of Banti's disease, and the spleen becomes considerably enlarged. The conditions included in this group of diseases are associated with the hæmorrhagic diathesis, and profound reduction in the platelet-count of the blood is usual. Thus in place of a normal platelet-count of 250,000 or upwards, the blood may show only 50,000 or even fewer platelets per c.mm. Whether this deficiency is the result of faulty production by the bone-marrow or is due to the excessive destruction of the platelets in the spleen is not known with certainty. Splenectomy appears to effect cure in some cases in spite of the fact that, following the operation, the rise in the platelet-count may be merely temporary and the original low level be re-established at a later date.

ADDISONIAN (or "Pernicious") ANÆMIA (p 652). In this the splenic enlargement is usually not great, and may be so slight that the spleen is not palpable clinically. In conditions of relapse, *e.g.*, from imperfect treatment, it is common for the spleen to increase in size. Microscopically, there is evidence of enormously increased phagocytic activity both in the spleen and in the bone-marrow (pp. 651–2 and *cf.* Plate XVII, p. 616). The reticulo-endothelial cells in each of these contain breaking-down red corpuscles and their pigment, and, in consequence, large amounts of hæmosiderin become stored. In the case of the spleen this storage can be demonstrated in the post-mortem room by means of the Prussian-blue reaction carried out with potassium ferrocyanide and hydrochloric acid, the splenic tissue becoming coloured a dark blue.

EGYPTIAN SPLENOMEGALY is an enlargement of the spleen which supervenes in some forms of *schistosomiasis* (pp. 392 and 695).

XANTHOMATOSIS OF THE SPLEEN :—

Gaucher's Disease (pp. 689, 1071 and 1263). This rare disease of the reticulo-endothelial system throughout the body, occurs usually in childhood, especially in Hebrews, sometimes in several members of the same family, and is characterised by a slowly progressive enlargement of the spleen, and, later, of the liver. The reticulo-endothelial cells, not only of the spleen and liver, but of the lymph-nodes and also of the bone-marrow, are affected, accompanied by slight anæmia with leucopenia : a brownish discoloration of the skin, and the formation of yellowish wedge-shaped areas in the conjunctiva. The enlargement of the spleen may be very great, the organ being tough and, on section, of a diffuse pinkish-grey colour. The pulp becomes largely replaced by masses of large rounded or irregular "Gaucher-cells," often multinucleated, and with faintly-staining fibrillar or reticulated cytoplasm. These cells represent the proliferated reticulo-endothelial cells of the spleen which have become packed with a material known as "kerasin," a cerebroside formed as a result of a combination of cholesterol with protein (p. 1071). Gaucher's disease is the only known condition in which this substance, kerasin, is formed. The material stains lightly with the ordinary stains for fat, but, with Weigert's special method for lipoids of complex type, the staining is intense. Other component parts of the reticulo-endothelial system which are especially affected are, as we have just noted, the lymph-nodes, liver and the bone-marrow ; and, in many of the cases, lipoidosis of the nerve-cells of the central nervous system is also found (p. 1071). The bones show changes which take the form of localised thickenings and rarefactions, so that pathological fracture may occur in the long bones, and the spine may exhibit angular deformity.

Niemann-Pick Disease. This condition is probably related to, and by some writers has been considered to be a rare form or variant of, Gaucher's disease. It has a similar incidence among Hebrew infants, but the disorder is a more serious one and the affected children rarely survive their second year. The spleen shows changes similar to those seen in Gaucher's disease, but the lipoid material is in this instance a phosphatide and is found in the mesodermal cells of the adrenals, thymus, kidney and pancreas, etc., as well as in the spleen and in the (ectodermal) nerve-cells of the brain and spinal cord (p. 1072).

SPLENECTOMY

The results of removal of the spleen have been studied experimentally in animals : and, in man, in cases of injury and in certain diseased conditions, more especially in splenic anæmia, in thrombocytopenia and in acholuric jaundice, both hereditary and acquired.

The organ is not essential to life and no serious effects have been observed after its removal, though this is generally followed by a transitory fall in the number of the red corpuscles, varying in degree and duration, but disappearing usually in from one to six months or a year. There is, however, sometimes an actual rise in the red cell-count. The erythrocytes also show a rapidly developed, and often persistent, increased resistance to hæmolysis by hæmolytic agents, as can be demonstrated experimentally, both *in vivo* and *in vitro*. The amount of the hæmoglobin is also diminished, and megalocytes may appear in the circulating blood. There is usually a distinct increase in the numbers of the leucocytes, somewhat variable in its amount and characters. The polymorphs are, as a rule, the principal cells to show such increase, but this may subside and be followed by a lymphocytosis, and also, it is said, by a characteristic increase in the eosinophils. Most important, however, is the effect upon the blood-platelets, for, after splenectomy, the counts show exceedingly large increases, sometimes to over 1,000,000 platelets per c.mm. The rise is usually not permanent, yet, in spite of this, the beneficial effects of splenectomy in reducing hæmorrhage in diseased conditions is not lost by the return to a lower platelet-count. In some instances, however, all these changes are comparatively slight, or even absent. Hyperplasia of the bone-marrow and also a slight increase in the size of the lymph-nodes have been described in some cases—the reticulo-endothelial system in these tissues taking on increased activity in blood-destruction, to replace that important function of the spleen. Splenectomy is of some value in cases of acholuric jaundice and thrombocytopenic purpura, and also in some, though not in all, cases of splenic anæmia, including Banti's disease (p. 696). Splenectomised animals may exhibit an increased susceptibility to certain diseases—for example in monkeys, after removal of the spleen, the inoculation of the spirillum of relapsing fever leads to a uniformly fatal result, in place of the regular, periodic attacks and possible recovery which follow in the case of the non-splenectomised animal.

CHAPTER XXI

DISEASES OF THE ALIMENTARY CANAL

SECTION I

DISEASES OF THE MOUTH

Malformations :—

Various clefts and fissures have been described in connection with the lower lip, the palate, and nasal bones, etc., but the most frequent developmental defects, in this region, are cleft-palate and hare-lip. These defects occur in the upper lip and palate, and the main features in the development of these parts are shown in the diagrams (Fig. 389).[1] Failure of union along the lines shown may result in anything from a slight cleft on one side of the mid-line to a complete failure of union of lip and palate. The hare-lip may be bilateral or "double" (Fig. 388), but this is less common than the "single," unilateral form (Fig. 387). The cleft-palate may occur by itself or together with the hare-lip, and the degree of cleft-palate varies from a bifid uvula to a complete V-shaped defect through both soft and hard palate, the point of the V being posterior. If there is accompanying hare-lip, the palatal cleft runs forwards into the hare-lip on one or on both sides.

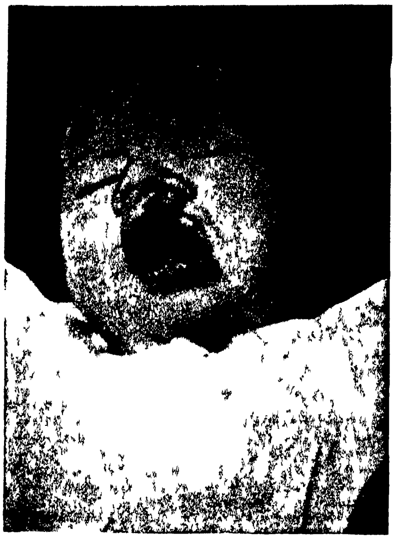

FIG. 387. Single hare-lip with cleft-palate. (From a case of Sir Harold Stiles and Carnegie Dickson, R.H.S.C., Edinburgh.)

Under the terms **Macroglossia** and **Macrocheilia,** congenital enlargements of the tongue and of the lips respectively are described. Macroglossia, or enlargement of the tongue, may occur in acromegaly, the enlargement being due partly to the thickening of the mucous membrane, and partly to the increase of the intermuscular cellular tissue. Lymphangiomatous enlargement, due to distension of the lymphatic spaces, with subsequent thickening and induration of the lingual tissue, is perhaps the most usual form of macroglossia. Muscular enlargement, due to an increase in the number and size of the muscular fibres, has been described in cretins and congenital idiots.

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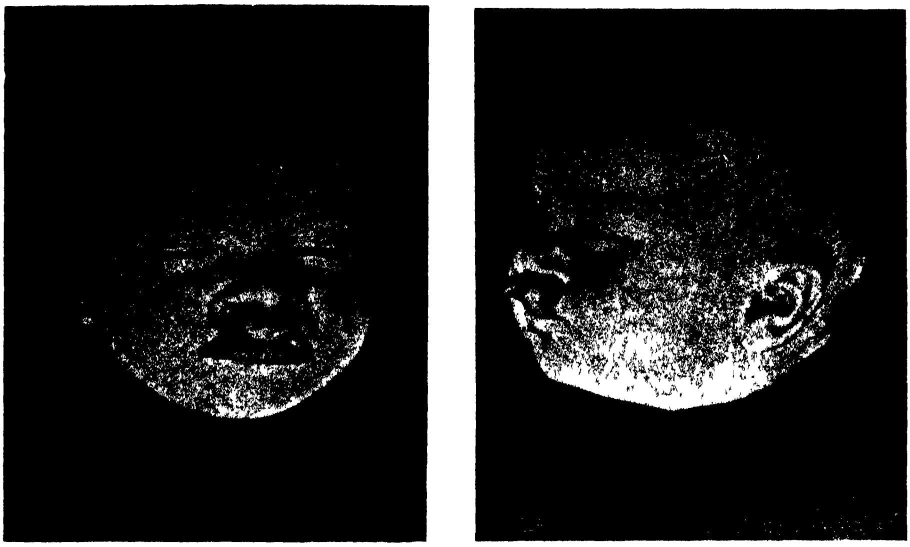
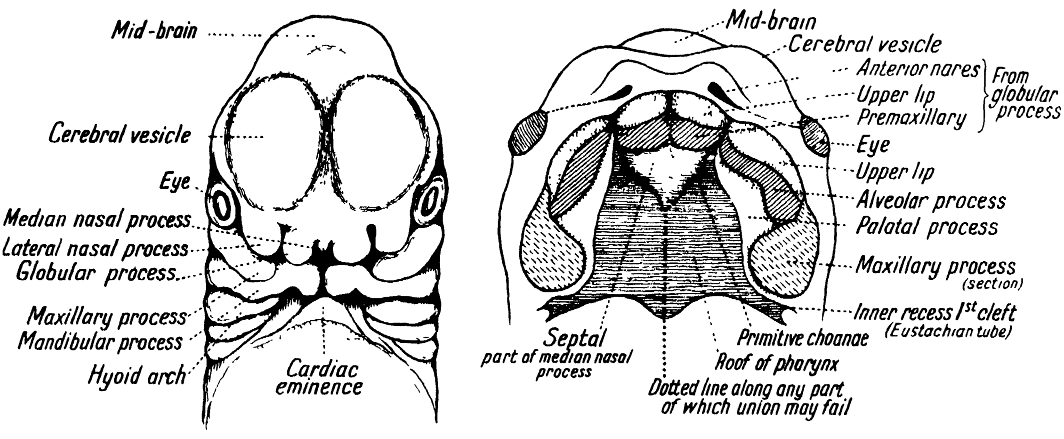
[1] For detailed descriptions of these and other malformations and deformities, the reader should consult "Human Embryology and Morphology," by Sir Arthur Keith, 5th edition, 1933.



(A) (B)

FIG. 388. (A) Double hare-lip, showing the premaxillary mass, etc., front view. (B) Side view of same showing projecting premaxillary mass.

(From a case of Sir Harold Stiles and Carnegie Dickson, R.H.S.C., Edinburgh.)



(A) (B)

FIG. 389. (A) Showing the formation of the face from the nasal, maxillary and mandibular processes in the embryo of the sixth week. (After His and Arthur Keith). (B) Showing the ingrowth of the palatal plates and maxillary processes at the end of the sixth week. (After Kollmann and Arthur Keith.)

In **Lymphatism,** the papillæ and lymphoid tissue at the root of the tongue are often considerably hypertrophied, a point of some importance in the diagnosis of the condition during life (pp. 686 and 839).

Abnormal fixation of the tongue—**Ankyloglossia**—may be due to imperfect development of the tongue or to a short and adherent frænum.

Degenerations :—

Amyloid degeneration has been described as present in the tongue in a few cases, causing marked enlargement of this organ. Fatty changes are seen in wasting diseases ; but both conditions are unimportant. In myxœdema, the degenerative changes are usually well marked in the tongue.

Atrophy of the tongue may be associated with degeneration in the nucleus of the hypoglossal nerve, *e.g.*, in bulbar paralysis.

Inflammation :—

Inflammation of the mucous membrane of the mouth (stomatitis) may be present in varying degrees.

(*a*) **Catarrh.** This condition is found in acute fevers, *e.g.*, typhus, typhoid, and scarlet fevers, etc., and it also arises from the irritation of carious teeth and similar causes. The mucous membrane becomes red and swollen, and there is a great increase in the desquamation of the surface epithelium, and also in lymph-transudation and leucocyte-emigration. The desquamated epithelium becomes mixed with the exuded fluid and the leucocytes, and a thick layer may accumulate, especially upon the tongue—" Furred tongue." In this " fur," various bacteria, mostly normal inhabitants of the mouth, are found in large numbers.[1] Frequently, the inflammatory process affects especially the mucous glands, so that prominent nodules or even vesicles are formed. This condition of follicular stomatitis may lead, by rupture of the vesicles, to follicular ulceration.

(*b*) **Aphthous stomatitis** or " **Thrush** " (*cf.* pp. 93 and 568) occurs principally in young and unhealthy children, but may also attack weakened adults. The condition is due to the presence of a fungus—*Monilia albicans*—and is distinguished by the presence on the mucous membrane, especially of the lower lips and gums, of irregular, opaque, whitish areas. These patches are more or less adherent, and are composed of masses of desquamated epithelium united by branching threads, consisting of the elongated cells and spores of the fungus.

(*c*) **Gangrenous Stomatitis (Noma or Cancrum Oris)** affects the mucous membrane of the cheeks in poorly nourished children, especially in those recovering from some severe illness, such as measles or scarlet fever. At first, there is seen on the outer surface of the cheek a diffuse swelling—firm and red, with, as a rule, a darker centre. The inner side of the cheek shows an intense inflammatory reaction, with, usually, a central irregular ulcer, at the base of which there is a dark sloughing mass. The condition spreads extremely rapidly, with extension to, and necrosis of, all the tissues of the cheeks and lips. It commonly involves the gums also, and even necrosis of the jaw may result. The advancing edge is always intensely red, and shows all the usual phenomena of inflammatory reaction in marked degree. Diphtheroid bacilli, fusiform bacilli, various spirochætes, leptothrix-like organisms, streptobacilli, and other bacteria, have been found in the necrosed and necrosing tissues ; but the specific pathogenic relationship of any one of these to the disease has not been established.

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[1] An extraordinary degree of hyperplasia of the filiform lingual papillæ (up to half-an-inch in length) has been observed by Carnegie Dickson, in a case of mycosis of the tongue, the organism associated with the condition being *Rhizopus niger*. The glossitis, in this case, was characterised by marked hyperkeratosis of the papillary filaments, and by blackish pigmentation—Melanoglossia.

(*d*) **Other forms of Stomatitis** may occur, giving rise to necrotic and ulcerative changes. In smallpox, the vesicles which form in the mouth may rupture and give rise to ulcers. In scurvy, due to vitamin-C and vitamin-P deficiencies (p. 443), the spongy swelling of the gums may result in ulceration around, and loosening of, the teeth, or even in necrosis of the bones of the jaw. In the severe form of stomatitis due to the prolonged absorption of mercury, there is always associated pyorrhœa, the mucous membrane of the gums and cheeks becomes much swollen, the teeth may become loosened and drop out, and extensive ulceration of the gums frequently follows.

Glossitis or Inflammation of the Tongue (*see also under* Catarrh, p. 704), most commonly arises as a result of injury from without ; but it may be produced by the irritation of carious teeth, or by the extension of a neighbouring erysipelatous area. The whole organ becomes swollen, and the tissues are infiltrated with inflammatory products, but suppuration very rarely occurs. The condition sometimes persists and assumes a chronic form, bluish-white, pearly patches—which may be smooth or warty, and are due to a hyperplasia of the epithelium, with usually some evidence of chronic inflammatory change in the deeper tissues—appearing on the tongue. To this condition, various names, such as leukoplakia, keratosis, psoriasis, tylosis and ichthyosis, have been given. **Atrophy** alone, or atrophy with a superimposed **glossitis,** is a common feature, and one of diagnostic value, in certain forms of anæmia. In **hyperchromic macrocytic anæmia** of Addisonian or so called "pernicious" type (p. 653), atrophy of the mucosa, often accompanied by atrophy of the muscle, may give the tongue a smooth glazed appearance. If glossitis supervenes, the tongue may be a fiery red colour. In the **hypochromic microcytic anæmia** of women (p. 644), especially elderly women, and in the tropical disease of **sprue** (p. 654), similar changes may be found in the tongue. In sprue there may be, in addition, pronounced atrophy of the walls of the stomach and intestines. Some cases of hypochromic microcytic anæmia have difficulty in swallowing—dysphagia—due to failure of relaxation of the pharyngeal muscles. The combination of anæmia, atrophy of the tongue, dysphagia, digestive disturbance and atrophic changes in the finger-nails, is known as Paterson's (or the so-called "Plummer-Vincent"[1]) syndrome.

Syphilis (p. 81 *et passim*) produces various lesions in the mouth. These are frequently secondary, but the primary chancre may occur in this situation, especially on the lips. Of the secondary lesions, the commonest are the mucous patches, flat condylomata, or warts, which frequently break down to form superficial ulcers. Gummata, if deeply situated, may cause extensive necrosis and ulceration, with considerable loss of substance of the tongue and neighbouring parts. The healing of these deep ulcers produces large areas of cicatrisation, which may lead to deformity of the tongue. Syphilitic glossitis is not infrequently followed by carcinoma of the tongue.

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[1] *See* footnote on p. 645.

Tuberculosis (p. 71) is comparatively uncommon in the mouth, and is usually secondary to affections of the pharynx or larynx, or to pulmonary tuberculosis. The ulceration, which sometimes simulates epithelioma very closely, occurs usually on the dorsum or at the margins of the tongue ; but tuberculous nodules may be found also at its root. Small nodular masses are formed, which undergo caseation, and sometimes ulceration. Lupus of the face may involve the mouth in its spread.

Leprosy (pp. 78–9). Nodular masses of granulation-tissue, similar to those found in the skin, occur in the mucous membranes of the mouth and tongue.

Actinomycosis and other mycotic infections may invade the tongue (pp. 91–2, and footnote on p. 704).

TUMOURS AND CYSTS :—

Simple tumours, such as fibromas, lipomas, myxomas, chondromas, and papillomas, occur in the submucous tissue of the mouth or tongue. Angiomas, composed of both blood-vessels (hæmangiomas) and of lymphatic vessels (lymphangiomas), are found on the lips, tongue or palate.

Sarcomas are rare, unless they have extended from other parts, *e.g.*, a periosteal sarcoma, growing from the jaw, may form a projecting mass in the mouth. **Carcinomas** are the most important tumours of the mouth. They are common, and are generally epitheliomas of squamous-celled type, their most frequent sites being the lower lip and the tongue (Fig. 166, p. 335).

Cystic formation, due to the blocking of the ducts of mucous glands, occurs in the tissues of the tongue and the lips, and one form (" ranula "), due to closure and distension of the duct of a mucous gland, or of the submaxillary or sublingual glands, occurs beneath the tongue (pp. 704–5 and 712). Dermoid cysts, due to developmental irregularities in the obliteration of branchial clefts, etc., may occur.

DISEASES OF THE TEETH

Only the very briefest reference need here be made to some of the commoner affections of the teeth, as they are described in text-books of surgery and dentistry.

1. **Developmental Errors.** One or more of the permanent teeth, especially the " wisdoms " or third molars, may fail to erupt, either from imperfect development or from malposition and impaction of one tooth upon another. In some such cases, the growth of the jaw does not keep pace with the growth of the teeth and so crowding and distortion of the latter occur. For the proper development and nourishment of the teeth, a suitable supply of the necessary vitamins, particularly vitamin D (p. 440), is essential.

2. **Caries** of the teeth consists in the gradual solution of the lime-salts, with softening and disintegration of the enamel and the dentine, and the formation of a somewhat granular, brown or brownish-black detritus. In this degenerated material, numerous spirochætes, *Bacillus acidophilus odontolyticus,* leptothrix-filaments and other bacteria are found, and are considered by some authorities as causal (*see also* p. 707 opposite). The bacteria probably act by producing acids, which attack thinned or fissured portions of the enamel. The destructive processes may penetrate to the pulp of the teeth, and there set up inflammation and suppuration, producing death of the tooth itself and secondarily, alveolar abscesses (gumboils), or even necrosis of the jaw. A common sequence is for infection to enter through a breach in the dentine, spread from the pulp along the root-

canal of the tooth to its apex, and there form an abscess. Such abscess is usually walled off by a layer of granulation-tissue. Somewhat similar formation of granulation-tissue around the root and socket of the tooth may arise insidiously without a previous acute infection. Inflammation, suppuration, and abscess-formation in the gums may occur independently of dental caries. (*See also under* Diseases of the Jaw, *below.*)

3. **Congenital Syphilis** gives rise to the characteristic "Hutchinson's teeth." The upper central incisors are narrow and pointed (peg-shaped), the cutting edge being smaller than the base of the crown, and having on it a well-marked crescentic notch.

4. **Tumours and Cysts.** The cement-substance occasionally shows a hypertrophic condition, sometimes described as an exostosis or osteoma. It is really the result of chronic inflammatory changes, and not a true tumour. **Odontoma** (p. 308) is the name given to a group of tumours which arise, as a result of maldevelopment, from teeth retained in the alveoli, or from the tooth-follicles.

Adamantinoma is a form of odontoma arising from the enamel-organ and composed of epithelium in masses, the outer zone being columnar in type, the inner reticulated—much as seen in the normal enamel-organ. It may invade and destroy the jaw and require free removal. An analogous "ectopic" or misplaced form of this tumour is found as one variety of suprasellar cyst (p. 308, 7, (1), (*i*): Fig. 190, p. 350 : and Figs. 472–3, pp. 817–18).

Dentigerous Cysts are produced by dilatation of the dental follicles (p. 308). These sometimes reach a large size. Teeth may grow from their walls.

DISEASES OF THE JAW

Inflammation :—

Diffuse periostitis may follow an injury, the irritation of a dental plate, sepsis or caries of the teeth, prolonged exposure to the fumes of yellow phosphorus, or the administration of mercury, and it is sometimes a sequel of one of the acute infective diseases. More commonly, however, the inflammatory condition is localised, forming an acute alveolar abscess : or a more chronic condition, such as pyorrhœa alveolaris. In the former, the infective agent generally gains entrance through a carious focus in a tooth, and, spreading to, and causing necrosis of, the pulp, infects the deeper parts of the socket, and passes out through the gum on a level with the apex of the affected fang or between the gum and the neck of the tooth. More rarely, the opening is into the antrum, or externally, through the cheek. **Pyorrhœa alveolaris** is usually at first confined to one or two teeth, especially the lower incisors. It is also seen round "crowned" or otherwise devitalised or "dead" teeth. Later, unless treated, it tends to spread until all the teeth have become involved. There is usually marked congestion of the gums and some hæmorrhage. With ulceration and destruction of the periodontal membrane, the alveolar margin is gradually absorbed, and pockets are left between the teeth and the swollen gum, pus collects in these and eventually the teeth may be exposed from crown to fang, and gradually drop out. Various authors attribute diseases of the joints such as osteo-arthritis, rheumatoid arthritis, etc., to the absorption of toxic material from septic lesions, *e.g.*, of the gums and jaws ; and, in the pyorrhœa associated with these arthritic affections, a varying admixture of streptococci, streptobacilli, fusiform bacilli, spirochætes, leptothrix and other filamentous organisms, and other bacilli and cocci, is usually present. In many cases, streptococci are the predominating organisms, and that pyorrhœa is often thus associated with rheumatic affections is worthy of note in considering the causation of rheumatism. Such infective lesions of the teeth, gums and tooth-sockets are, moreover, often associated with various forms of vitamin-deficiency and constitute a prominent feature of diseases such as scurvy (p. 443), as well as with various metallic poisonings, *e.g.* with lead, arsenic or mercury.

Inflammatory and necrotic changes due to *Actinomyces* are found in the jaw (p. 91).

Necrosis :—

This may result from the inflammatory conditions already noted, and usually starts as a periostitis. The lower jaw is more frequently and more severely attacked than the upper. Necrosis may be secondary to injury (especially compound fracture), to some of the acute infective fevers such as measles, scarlet fever, typhoid fever or smallpox, to syphilis, to cancrum oris, or to the now comparatively uncommon conditions of mercury- and phosphorus-poisoning (p. 1205). In untreated or imperfectly treated cases of syphilis, the necrosis may be extensive, the palatine process of the superior maxilla being particularly liable to be involved and the destructive change to extend to soft palate and fauces.

Tumours and Cysts :—

Reference has already been made to tumours and cysts connected with the teeth and their sockets. Of the tumours of the jaw, the most important are the sarcomas and carcinomas. The sarcomas are usually of the round- or spindle-celled variety, and commence from the periosteum of the jaw or in the wall of the antrum. The carcinomas may be squamous-celled growths taking origin in the gum or palate, or of columnar-celled type commencing in the glandular tissue of the nasal or antral cavities. Tumours of the lips or of the tongue may spread to and involve the jaws. Of tumours of the gums and jaws, the so-called "epulis," simple or malignant, is the commonest. This is a somewhat indefinite term [1] which has been applied to various tumours and other lesions projecting through or from the gums, including simple fibromas, the border-line giant-celled osteoclastoma ("myeloid epulis"), and the malignant periosteal sarcomas. In connection with the jaws, various other tumours are found, such as odontomas (p. 308), chondromas, and osteomas (p. 303 *et seq.* and p. 1225 *et seq.*).

DISEASES OF THE SOFT PALATE, PHARYNX, AND TONSILS [2]

Diverticulum of Pharynx. This condition is uncommon. The pouch arises from the posterior wall of the pharynx, its orifice being situated opposite the cricoid cartilage. It is produced by a gradual evagination of the mucous and the submucous coats of the pharynx between the two parts of the inferior constrictor muscle. The pouch is at first small, but gradually enlarges. The diverticulum may become filled with food, undergo further enlargement, and eventually come to press upon and obstruct the œsophagus.

Inflammation :—

Without necessarily causing any inflammatory changes, various potentially pathogenic micro-organisms or the milder varieties of these (p. 503), may inhabit the naso-pharynx. Thus, type-I meningococci may be recovered from the throats of persons, *e.g.*, nurses, who have been exposed to infection, and thus become " carriers " (pp. 981–2). Similarly, the virus of poliomyelitis may exist in the naso-pharynx (pp. 105–6).

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[1] "Epulis": an old-fashioned if convenient term for a lesion, usually a tumour, "on the gums," from the Greek ἐπουλίς, *epoulis*, originally a "gum-boil" (ἐπί, *epi*, upon, and τά οὖλα, *ta oula*, the gums).

[2] *See also* Diseases of the Nasal Cavities and Naso-Pharynx, p. 502 *et seq.*, in Chapter XVII, Diseases of the Respiratory System.

Acute inflammation in the soft palate, pharynx and tonsils is sometimes described clinically under the term " angina." The reactions are similar to those of inflammation in other areas and their special characters depend largely on the looseness of the structures and the presence in this region of an abundance of lymphatic tissue, which is distributed in the form of isolated rounded masses resembling the solitary follicles of the intestine. Congestion and œdematous swelling are usually marked features of such inflammation.

(*a*) **Catarrh,** in its acute form, is generally the result of invasion by pyogenic cocci—staphylococci, streptococci and pneumococci—the bacillus of diphtheria or diphtheroid bacilli, Pfeiffer's bacillus and other bacteria ; though it may be caused, or a suitable nidus for these organisms be prepared, by irritation, *e.g.*, by hot liquids, chemicals or exposure to cold. It is particularly common in acute infections—many of the infective diseases having, for their first symptom, " sore throat " or pharyngitis. The mucous membrane becomes reddened and swollen, and, at a later period, is covered with a mucous exudate. Sometimes small vesicles develop, and these, by their rupture, lead to ulceration.

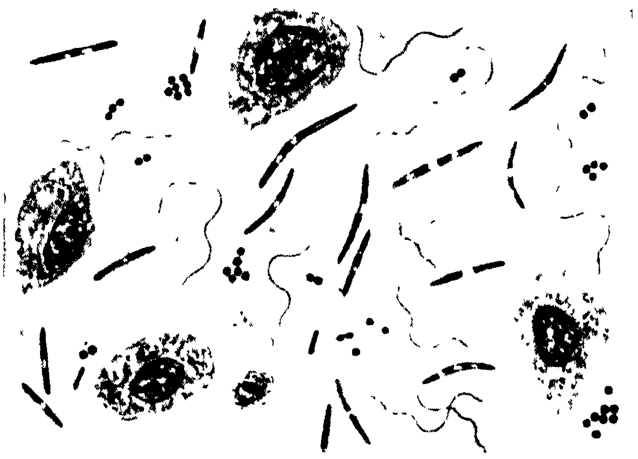

FIG. 390. *Vincent's Angina.* Film from exudate of ulcer on tonsil, showing spirochætes, *B fusiformis*, etc. × 1000.

(*b*) **Chronic catarrh** may follow repeated acute attacks, and is of frequent occurrence in people who use the voice excessively, and in smokers. In the earlier stages, the mucous membrane is thickened ; but, later, it may become indurated and atrophic. " Granular " elevations are frequently seen, these being either distended mucous glands or proliferated lymph-follicles. The term **" granular pharyngitis "** has been applied to this condition.

(*c*) **Acute suppurative or " phlegmonous " pharyngitis** is characterised by the mucous membrane and the submucous tissues being involved in an acute inflammation, which later becomes suppurative. The soft palate, uvula, tonsils, and other adjacent structures may be much swollen, deeply congested and œdematous. The œdema often extends to the loose structures of and around the epiglottis, and sometimes œdema glottidis may supervene. The disease is almost always bacterial in origin, various streptococci being the organisms most frequently isolated from such cases. Other bacteria, however, may also produce the condition. Retropharyngeal abscess may follow, but this may also be a complication of certain of the infective fevers, tuberculosis of the faucial or pharyngeal mucous membrane, tuberculous caries of the spine, or, in some cases, degenerative and suppurative changes in the retropharyngeal lymph-nodes.

(*d*) **Vincent's Angina** (p. 374). This is an acute inflammation of the pharynx and tonsils which may be characterised by the formation of a firm yellowish-white false membrane, very similar to that seen in diphtheria. All degrees of ulceration may occur ; in some cases it is merely superficial, whilst, in others, usually accompanied by extensive œdema, it may be the most prominent feature, and a soft, necrotic foul-smelling false membrane may be produced.

Similar ulcerative and " membranous " conditions may be found on the cheeks, gums or palate, giving rise to **necrosing inflammations, ulcerative stomatitis** and **noma.** The association of fusiform bacilli with this special type of inflammation was first recognised by Vincent (1896). Spirochætes are always present also. It has been frequently shown that both fusiform bacilli and the spirochætes may be found in the secretions of the mouth under " normal " conditions, and may be present in considerable numbers in cases of true diphtheria. Similar organisms are found in catarrhal and other inflammatory conditions of the mouth and fauces. They are often found in the tonsillar crypts, with or without inflammatory changes. Vincent's angina is frequently present in cases of agranulocytosis (*q.v.*, p. 636).

(*e*) **Diphtheria** begins usually in the mucous membrane of the tonsils, and may spread to the fauces, the uvula, the posterior wall of the pharynx, and to the nares, the larynx, and the trachea, and even, in rare instances, down the œsophagus. At first, the tissues of the fauces are hyperæmic and swollen. Later, greyish or yellowish patches, somewhat resembling wash-leather, make their appearance, and generally coalesce into a definite false membrane. The underlying tissues become infiltrated with inflammatory exudate, and, when the false membrane is removed, a raw, bleeding surface, with varying degrees of necrosis is seen. The lesion may vary in intensity from a catarrhal inflammation to extensive necrosis and ulceration. On microscopical examination, the false membrane is found to consist of necrotic mucous membrane and masses of fibrin, entangling leucocytes and degenerated epithelial cells. On the surface, there are accumulations of debris, containing large numbers of organisms, especially various kinds of cocci, in addition to the diphtheria bacillus itself. In the later stages of the disease, there may be extensive necrosis of the mucosa and submucosa. The causal organism is *B. diphtheriæ* (*Corynebacterium diphtheriæ*) which, owing to its potent exotoxin, produces local necrosis in the throat and, by diffusion of the toxin, lesions in the heart-muscle (p. 469), kidneys (p. 868) and nervous system (pp. 1183–4). Associated with the inflammatory reaction in the pharynx, there is frequently some enlargement of the lymph-nodes at the angle of the jaw and elsewhere in the neck. In some cases, this swelling may be severe, and is generally associated with the presence of strepto- or staphylo-cocci.

(*f*) **Tonsillitis** may be acute or chronic. In the acute form, the surface is usually marked with small whitish spots, which are produced by the degeneration of the epithelium in the lacunæ or crypts of the tonsil. There is, in addition, inflammatory swelling of the tissues ; and ulceration or suppuration may supervene in the tonsil itself, or, more frequently, in the alveolar tissue of the soft palate above the tonsil, giving rise to the peri-tonsillar abscess or **quinsy.** In the chronic form, the tonsils are, in most cases, enlarged, both from hypertrophy of the lymphatic follicles and from increase in the interstitial connective tissue. This chronic proliferative overgrowth is due to repeated acute or subacute attacks. Blockage of the lacunæ may cause obstruction and retention of the contents, which often become inspissated, and even calcified. Tonsillar calculi so formed are usually small, but in a case seen by one of the authors, a calculus about the size of a walnut was removed by operation.

In association with this chronic enlargement of the tonsils, there is frequently proliferation of the lymphoid follicles of the pharynx. To this condition—especially when occurring in the roof of the nasopharynx in young subjects—the term adenoid growths or "adenoids" has been given (p. 503).

Syphilis (*see* p. 80 *et seq.* Granulomata).

Tuberculosis (pp. 56 and 68, Tuberculosis of Lymph-Nodes).

Tumours. Sarcomas, which may commence as polypi, are found in the naso-pharynx ; and the tonsils may be the seat of lympho- and of mixed-celled sarcoma. Squamous epithelioma may occur in the tonsil and also in the region of the epiglottis. The so-called "lympho-epithelioma" (p. 339) is found especially in the pharyngeal and tonsillar tissues.

DISEASES OF THE SALIVARY GLANDS

Inflammation :—

EPIDEMIC or INFECTIVE PAROTITIS (Mumps) (p. 117) is a specific disease due to a filtrable virus which may be recovered from the saliva of patients suffering from the disease. Infection of one or both parotid glands occurs, and the other salivary glands may also be affected. The parotid gland becomes swollen, tense and painful, but in an uncomplicated case there is no suppuration, and, as recovery supervenes, the condition of the gland soon returns to normal. The testicle or ovary may become involved also, with swelling and pain as in the case of the parotid. Complete recovery is the rule though occasionally atrophic changes follow. Mastitis and pancreatitis are occasional complications ; and a meningitis, or meningo-encephalitis, with excess of lymphocytes in the cerebrospinal fluid, is not infrequently present (p. 117).

Inflammation of the parotid and other salivary glands may be a secondary complication of diseases such as typhoid and other infective fevers ; or the infection may result from the pyogenic organisms which are common inhabitants of the mouth. There may be suppuration in the glands.

In **pyæmia,** abscess in the parotid may be found as part of the general blood-infection.

Angina Ludovici (Ludwig's angina—p. 505) is an intense inflammatory reaction, often with abscess-formation, which occurs occasionally in the floor of the mouth, and in the tissues in and around the submaxillary gland, *e.g.*, in cases of scarlet fever. A similar condition sometimes results from the spread of infection from carious and suppurative processes at the roots of the teeth.

Salivary calculi are commoner in the submaxillary and sublingual glands than in the parotid. They are usually produced by a deposit of lime-salts in the thick mucous secretion and desquamated cells following inflammation of the ducts, and are generally single, but may be multiple. Such calculi may be formed in the ducts either within, or external to, these glands.

Tuberculosis, Syphilis, and **Actinomycosis** rarely produce local lesions in the salivary glands, but cases of each have been recorded.

Mikulicz's Disease. In this rare condition, there is a symmetrical enlargement of the salivary and lachrymal glands on both sides—and, in some cases, of the labial and buccal mucous glands. The enlargement begins in early adult life and is progressive. Some authors regard it as a granulomatous condition, whilst others consider it leukæmic or lymphadenomatous. It is true that enlargement of these glands may occur in leukæmia and in Hodgkin's disease, but in Mikulicz's disease proper there is no involvement of the lymphatic system and no blood-changes. No relationship to syphilis or tuberculosis has been demonstrated. A familial form of enlargement of these glands has also been described.

Tumours and Cysts :—

Cystic dilatation of the salivary ducts, sometimes associated with the presence of concretions or calculi in the ducts, gives rise to ovoid or rounded swellings containing viscid fluid (pp. 354 and 706). Tumours are rare, but fibromas, lipomas, hæmangiomas and lymphangiomas, and chondromas are found.

A rare tumour of the parotid and submaxillary salivary glands is the "**adenocystoma lymphomatosum**" or "**adenolymphoma**"[1] found mostly in middle-aged or elderly males. Almost always a slow-growing simple tumour, it has a thin, dense fibrous-tissue capsule, and its cut surface is either more or less solid or shows cystic spaces and clefts, often containing branching papillomatous projections, lined and covered respectively by tall columnar non-ciliated epithelium with a fine eosinophilic cytoreticulum containing innumerable minute oxyphil granules, and a characteristic row of spherical or ovoid nuclei near the free margins of the cells. Beneath this more or less uniform layer is a less regular layer of basal cells ; and, external to a thin basement-membrane, is a delicate reticulum containing small lymphocytes, plasma-cells and numerous lymphoid follicles—this lymphadenoid tissue participating with the epithelium in the formation of these tumours.

The commonest tumour in the parotid gland is one composed of a mixture of adenomatous tissue and cartilage in which myxomatous degeneration is liable to take place—the so-called myxo-chondro-adenoma (pp. 291, 306 and 351). This tumour is now usually designated as a "**mixed salivary-gland tumour,**" for considerable doubt exists as to the pathogenesis of its histological elements. Attempts at operative removal are oftentimes inadequate, so that recurrences are frequent. In its recurrences this neoplasm becomes less differentiated, and finally either carcinoma or sarcoma may develop. Similar tumours may be found in other salivary glands. Apart from those originating in the mixed tumour, sarcomas and carcinomas also occur.

DISEASES OF THE ŒSOPHAGUS

Developmental Abnormalities, Malformations, etc. :—There may be **atresia**[2] of the œsophagus, the undeveloped part being usually at the level of the lower end of the trachea ; above the site of the lesion, the œsophagus may be dilated and hypertrophied ; below, it is atrophied. It may open into the trachea or into one of the main bronchi. These conditions are found at birth and are not compatible with continued life. They are due to maldevelopment of the septum between the œsophagus and trachea (Fig. 391).

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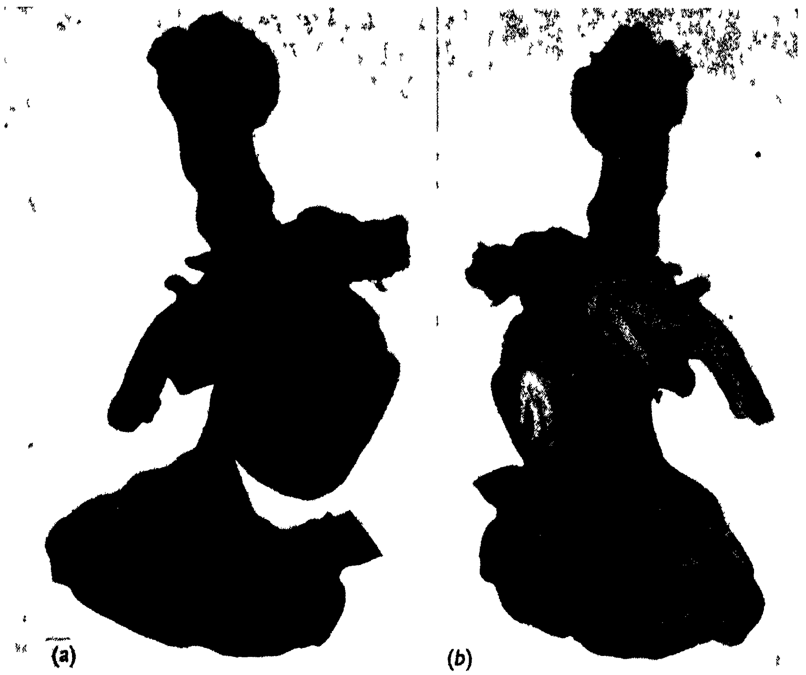
[1] "Adenolymphoma of the Salivary Glands," by Matthew J. Stewart *et al.*, *Jour. Path. and Bact.*, 1935, **40,** 601 : and "Adenocystoma Lymphomatosum of the Salivary Glands," by P. N. Harris, Boston, Mass., *Amer. Jour. Pathol.*, 1937, **13,** 81.

[2] "Atresia," without an opening or canal, from Greek, ἀ-privative, and *τρῆσις, trēsis,* a perforation or opening (*cf. τρημάτώδης, trēmătōdēs* (p. 383), having a perforation, opening or vent to the intestinal canal).



(A) (B)

FIG. 391. Malformation of œsophagus in an infant

In (A), posterior view, the upper third of the œsophagus (which has been slit open vertically) is much hypertrophied and ends at the level of the bifurcation of the trachea, with which it communicates by a small opening. There is absence of the middle portion of the œsophagus and the lower half begins in tapering fashion and continues normally to the stomach In (B) anterior view, the trachea is opened to show the communication at its lower end (marked by a rod) with the upper portion of the œsophagus

An anterior diverticulum of the œsophagus is sometimes found near the bifurcation of the trachea, opposite the site of the bronchial lymph-nodes. Such diverticula are usually small and conical, and are produced by traction on the œsophagus by adhesions which have been formed between it and diseased bronchial lymph-nodes. Ulceration and perforation may supervene, giving rise to septic infection of the pleura, pericardium, or lungs (Fig. 392).

Dilatation of the œsophagus may be throughout its whole length or in the lower part only ; the latter form is seen in children with congenital pyloric stenosis and is, as a rule, combined with hypertrophy of the muscle of the wall. In adults, the dilatation may result from stricture at the lower end, due to tumour or scar. Cases also occur with no anatomical obstruction and in these the cause is obscure. It may be spasm of the muscle of the cardiac end of the œsophagus or lack of relaxation of its tone—“ **achalasia** ”[1] (pp. 715, 716–17, 734 and 1190).

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[1] “Achalasia,” non-relaxation, from Greek, ἀ-privative, and χαλάω, *chalaō*, I relax, hence ς, *achalastos*, unrelaxed.

Circulatory Disturbances:—**Chronic venous congestion** of the mucous membrane is found in diseases of the heart or lungs, or in cirrhosis of the liver. In the last of these, owing to obstruction of the circulation through the portal vein, the œsophageal veins at the lower end of the tube become varicose, and the mucous membrane over these varicosities may undergo ulceration. The ulcers are usually small, deep and terraced, and they sometimes open into the veins and give rise to serious and even to fatal hæmorrhage.

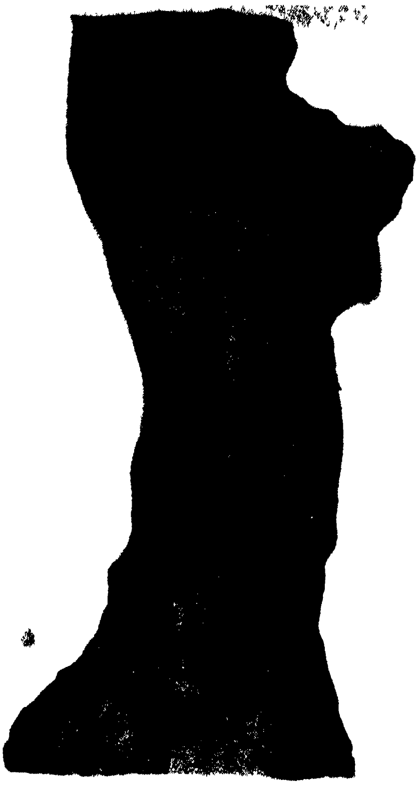

FIG. 392. Œsophagus with several diverticula. One, about the centre of the specimen, is clear cut and oval, the others are puckered. These were due to tuberculous foci invading the outer part of the œsophagus. The lowest diverticulum was ulcerated and an adjacent blood-vessel had been eroded, causing a fatal hæmorrhage. From a middle-aged male.

Inflammatory and Necrotic Conditions:—Inflammatory changes of a more or less severe character, with necrosis of the mucous membrane, may result from the ingestion of corrosive acid or alkaline liquids, from scalding, or from the impaction of foreign bodies such as dentures, bones, safety-pins, coins, the bone-plates of babies' teats, etc. In these, ulceration and perforation, giving rise to abscess-formation, cellulitis, pleurisy, or empyema, may supervene. The slough produced as a result of the ingestion of corrosive acid may become detached and reach the stomach, and then be vomited as a " cast." Ulceration is sometimes found in cases where the cause remains obscure. Pringle and Teacher (1919) have reported several cases of post-operative hæmatemesis, in which lesions varying from superficial erosion of the interior of the œsophagus to perforation or widespread destruction of the tube and damage to adjacent structures were found. They deduced that these lesions had taken place during life from the fact that hæmorrhages had occurred into the œsophageal wall, lungs and pleuræ, and also because, in one of their cases, inflammatory phenomena were present in the lungs and pleural sac. They conclude that digestion of the œsophagus may occur during life and be one cause of post-operative hæmatemesis. If there has been severe damage with considerable loss of substance during the inflammatory or ulcerative process, cicatricial contraction producing stenosis may be a result of the excessive reparative processes in the damaged area. Thus, one or more localised fibrous strictures may be formed.

Post-mortem digestion of the lower end of the œsophagus is common, and all degrees, from superficial erosion of the lining cells to actual perforation, are seen. The absence of inflammatory reaction serves to differentiate this condition from pathological changes which have occurred during life.

Stenosis of the œsophagus from cicatricial stricture has been mentioned above.

Contraction of the upper end of the œsophagus may be due to an abnormal tonicity of the upper sphincter, or to a fibrous replacement of the muscle-fibres in that sphincter, with, perhaps, the production of a fibrous stricture. Congenital stenosis of the mid-part of the œsophagus—from the level of the bifurcation of the trachea to within one or two centimetres of the diaphragm —has been recorded. Stenosis is sometimes due to pressure by aneurysm. Malignant stricture is described below under tumours of the œsophagus, as are also the secondary phenomena produced in the œsophagus itself by such constrictions. In many cases in which during life there had been clinical evidence suggesting an obstructive lesion, little or no narrowing of the œsophagus is found after death. Such cases are due to irritative muscular spasm, or, in some instances, the phenomena have been of nervous origin (*see also* p. 713, " Achalasia ").

Tumours :—The occurrence of fibromas, lipomas, and myomas has been described, but these are rare. Papillomas are commoner.

The most important tumour of the œsophagus, however, is carcinoma. The growth is, in nearly all cases, a **squamous-celled epithelioma.** A tumour of this nature may occur in the pharynx or in any part of the œsophagus, and, though its most usual situation is the upper third, it is found almost as often in the middle third, where the left bronchus crosses the œsophagus. Starting at one point, it spreads circularly round the wall of the tube, the growth in some instances being localised, in others spreading widely and infiltrating the mucous and submucous coats and later invading the deeper parts. Dilatation of the tube, with hypertrophy of the muscular coat, may occur above the tumour, if obstruction is present ; but, even with comparatively large projecting tumours, there may sometimes be little or no obstruction. In some cases in which the opposite wall of the œsophagus lies in contact with the tumour, a " contact " epithelioma develops. Ulceration may take place and communication between the œsophagus and the surrounding parts be established. The lymph-nodes in the neighbourhood may be invaded secondarily and small metastases are found occasionally in the pericardium.

Glandular carcinomas are rare as primary growths; sarcomas also are extremely rare ; but the extension of a tumour from the stomach coming to involve the œsophagus is not uncommon. Infiltration of the œsophagus and neighbouring structures by bronchial carcinoma is comparatively common.

SECTION II

DISEASES OF THE STOMACH

In studying diseases of the stomach, it is important to remember that interference with its normal structure will cause derangement of its function, and that this will aggravate the pathological condition which is present. Thus, any disease of the stomach will interfere with the function of the gastric glands, and the contained food will remain imperfectly digested, and will undergo decomposition. The products of such decomposition—acetic, lactic, butyric acid, etc.—cause further irritation of the mucous membrane, and the gases formed during the process produce distension of the viscus and interference with its peristalsis.

Post-mortem Changes :—

Decomposition in any food-contents of the stomach occurs very soon after death ; and the decomposition-products, acting on the mucous membrane, cause it to assume a reddish or greenish colour, which, later, becomes slaty-blue or almost black, owing to chemical alterations in the blood-pigment. Thus, vascular and other changes which may have been present during life are often obscured.

In some cases in which death has taken place during active digestion, or while the gastric juice was still being secreted, digestion of the coats of the stomach itself is observed. In this condition of **post-mortem digestion** or **cadaveric softening**, the mucous membrane becomes swollen, softened, and digested away, and the muscular and peritoneal coats may be perforated. This post-mortem change is, as a rule, found in the neighbourhood of the fundus, generally on the posterior wall near the cardiac end—that is, in the situation on which the stomach-contents lie when the body is in the dorsal position. The softened area is frequently extensive, its edges are usually much thinned—sometimes resembling tissue-paper—and may be shred-like, and there is no evidence of any inflammatory action in the neighbourhood. The stomach-contents escape and are found free in the peritoneal cavity. The condition is differentiated from ante-mortem perforation or rupture of the stomach by the absence of peritonitis or any thickening or inflammation at the margin of the perforation, but it must be remembered that post-mortem digestion may be superimposed upon previously present pathological conditions and give anomalous appearances.

Malformations :—

(*a*) **Hour-glass contraction** of the stomach is a moderately common condition, the contraction being situated usually about the middle of the organ. In the majority of cases, it is due to chronic inflammatory and cicatricial changes following ulceration (Fig. 393 and p. 724), or to infiltration and contraction produced by carcinomatous tumours. More rarely, it is caused by the contraction of peritonitic thickening or adhesions on the outer wall of the organ. There are, however, cases in which the condition is due apparently to the permanent contraction of the so-called mid-gastric sphincter, which, according to various observers, is usually active only during digestion, and marks the boundary between the cardiac and pyloric portions of the stomach. The condition of hour-glass contraction of the stomach has to be carefully differentiated from stricture in the duodenum with dilatation of its first part.

(*b*) **Atresia,**[1] or complete absence of lumen of the pylorus, is a rare congenital abnormality.

(*c*) **Congenital hypertrophic pyloric stenosis** is not uncommon. Its occurrence is ten times more frequent in boys than in girls, and it affects especially the first-born sons of families, the symptoms beginning to show usually from about the first to the sixth week after birth, though the condition may persist into adult life. In most descriptions there is said to be great hypertrophy of the muscular layer, particularly the circular fibres of the pyloric sphincter, the thickening being often palpable during life as a hard mass in the epigastrium or right hypochondrium. Some writers, however, for example J. Douglas,[1] believe that the circular fibres of the true sphincter remain unaffected, and that the hypertrophy is of both the circular and the longitudinal muscular fibres of the pyloric portion of the stomach up to, but not including, the circular fibres of the pyloric sphincter itself. There is usually also associated dilatation and hypertrophy of the œsophagus, especially towards its lower part. Hypertrophy of the cardia (with dilatation of the œsophagus above it), and of the ileo-cæcal sphincter, have been described as also occurring in some cases, in association with congenital pyloric stenosis, as well as independently of it. Various explanations of these localised hypertrophies of the gastric and intestinal sphincters, for example, achalasia (*see* footnote on p. 713) due to inco-ordination from abnormalities of innervation, hyperadrenalism, etc., have been suggested. The obstruction at the pylorus, which may be aggravated by œdematous swelling of the mucous membrane, causes vomiting of all food, and the child becomes emaciated from lack of absorption of especially proteins and of fluid and dissolved salts, and death may ensue if surgical treatment is not adopted. In some cases, the condition appears to be largely one of superadded spasm, which relaxes under suitable medical management, especially the administration of eumydrine (methyl atropine nitrate).

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[1] *See* footnote on p. 712.

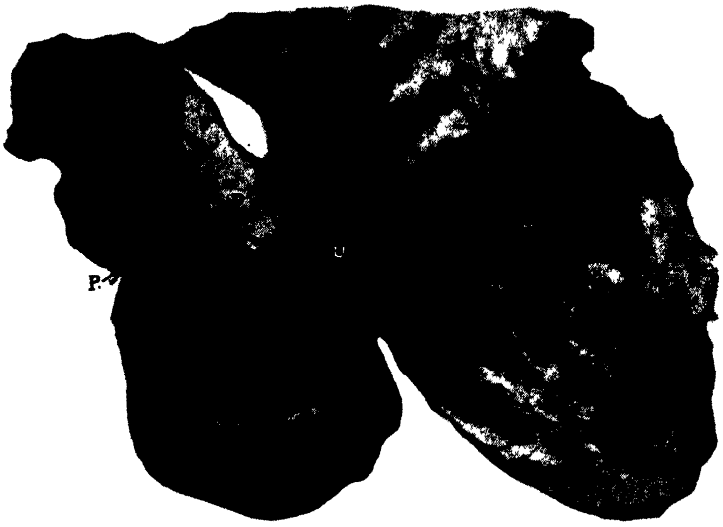

FIG. 393. "*Hour-glass constriction*" *of stomach*, the result of cicatricial contraction following upon a chronic peptic ulcer (U). The position of pylorus is marked (P.P.).

Malpositions :—

Anterior displacement on account of defects in the anterior abdominal wall may occur. **Downward displacement** or **gastroptosis** is common, and may be congenital, or the result of dilatation of the stomach, or of traction on it by inflammatory adhesions. In cases with **transposition of the viscera,** the stomach may have its position reversed, the cardiac end of the organ being towards the right side (Fig. 251, p. 447).

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[1] M.D. Thesis, University of Edinburgh, July, 1935 (quoted by Sir John Fraser, *The Medical Annual*, 1936, p. 373).

Bezoars and Concretions.[1] Intra-gastric foreign bodies and matted concretions of hair ("trichobezoars") or of vegetable fibres ("phytobezoars"), especially of persimmons or American date-plums, or consisting occasionally of resins or balsams precipitated from alcoholic solution (*e.g.*, spirit-varnish containing shellac) are found most usually, though not exclusively, in psychopathic patients. Descriptions of these cases and their treatment will be found in textbooks of surgery and mental disease. Such concretions may cause irritation and interference with function, obstruction, erosion, ulceration and perhaps even perforation, with resulting peritonitis. Similar concretions in the stomach or intestine are common especially in hairy or furred animals such as cats and goats and cattle.

Circulatory Disturbances :—

(*a*) **Acute congestion** is seen as an early stage of inflammation of the mucous membrane, or may result from irritating food or irritant poisons.

(*b*) **Chronic venous congestion or passive hyperæmia,** is a comparatively common finding *post mortem*. It may arise secondarily to obstructive disease of the heart, but especially as a result of obstruction of the portal circulation by cirrhosis and other diseases of the liver. The mucous membrane is reddened and œdematous, and minute hæmorrhages are frequently found in the submucous tissues. Over these hæmorrhages, the mucous membrane often becomes eroded by being digested by the gastric juice, and small ulcers—**hæmorrhagic erosions**—are produced (Fig. 394, p. 720). These hæmorrhages and erosions are frequently present in considerable numbers, especially towards the pyloric end. After healing, they may be represented by small areas of atrophy and may be pigmented. Chronic catarrhal changes are usually present in such cases.

(*c*) **Hæmorrhages** into or from the mucous membrane arise from a variety of causes. Simple gastric ulcers, or cancerous infiltration, by invading and opening into vessels, may give rise to any degree of bleeding, from slight oozing of blood up to very severe hæmorrhages, often with vomiting of blood —**hæmatemesis.** In acute yellow atrophy of the liver (acute liver-atrophy), purpura, scurvy, septicæmia, hæmophilia, and some of the acute fevers, *e.g.*, yellow fever and typhus : in chloroform- and phosphorus-poisoning, and in severe forms of anæmia and other "blood-diseases," hæmorrhage results, probably from fatty or other degenerative changes in the vascular endothelium, with subsequent rupture of minute vessels. In certain forms of cardiac disease, and in cirrhosis of the liver, distension of the gastric and œsophageal veins caused by venous obstruction, is a striking feature. In such cases, rupture of the distended veins, or ulceration over and extending into them, may lead to hæmorrhage (p. 714).

Except where an ulcer has opened into a comparatively large vessel, in which case pure blood may be vomited, the escaped blood becomes mixed with the contents of the stomach, is dark brown or almost black in colour, and is vomited in a semi-digested condition (" coffee-ground vomit "), or is passed down the intestine to appear in the fæces as black altered blood (melæna). Minor degrees of bleeding may be detected in the fæces only by the delicate tests for " occult blood."

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[1] "Bezoars and Concretions : A Comprehensive Review of the Literature, with the Analysis of 303 Collected Cases and a Presentation of 8 Additional Cases," by M. DeBakey and A. Ochsner, New Orleans, *Surgery*, St. Louis, 1938, **4,** 934, and 1939, **5,** 132. The word "bezoar" is derived, through the Spanish *bezaar* and the Arabic *bāzahr*, from the Persian *pād-zahr*, counter-poison, *zahr*, poison, because, in the Middle Ages, such concretions were believed to be antidotes to poisons. A familiar example of a "bezoar" is the "ambergris" which collects in the alimentary canal of the spermaceti-whale.

INFLAMMATION (GASTRITIS)

On account of the stomach being so much exposed to irritation, gastritis in varying degree is common. The acute form is apt to occur in connection with many of the acute infective fevers, from the swallowing of irritant poisons, or even after mere exposure to cold. It may be due to surfeit, or the ingestion of irritating and indigestible foods. If the condition is severe, the mucous membrane becomes swollen, reddened and softened, and shows minute hæmorrhages, or even hæmorrhagic erosions, especially towards the pyloric end. It is covered with viscid, tenacious, and perhaps blood-stained mucus. When due to the ingestion of **irritant poisons,** *e.g.*, arsenic, the inflammatory reaction is most pronounced along the prominent parts of the rugæ, or where the stomach-walls are in contact with one another. Where the poison is corrosive in character, the mucous membrane is discoloured, nitric acid giving a green, sulphuric acid a black, and carbolic acid a dark brown colour. Mercuric chloride (corrosive sublimate) produces a grey, coagulative necrosis of the mucosa. Strong caustic alkali causes swelling and softening of the stomach-wall. Necrosis may occur and lead to perforation of the stomach ; or there may be swelling, hæmorrhage and membranous inflammation with ulceration.

(*a*) **Diffuse suppurative or phlegmonous gastritis** is uncommon. There is intense redness and swelling of the mucous membrane due to acute inflammatory changes, which terminate in a diffuse infiltration of the mucous and submucous tissues with pus. Sometimes minute abscesses form, and these may rupture into the cavity of the stomach. The condition may start from an ulcer, or be superimposed on carcinoma of the stomach, but often its origin is obscure. It is generally associated with the presence of one of the varieties of streptococci.

(*b*) **Chronic catarrh** frequently results from repeated acute attacks, or it may be due to improper feeding. It is a usual sequel of chronic venous congestion and other diseased conditions of the stomach, and in many cases is caused by the swallowing, over prolonged periods, of infective material from the nose, mouth or throat or from the bronchi and lungs.

The stomach is usually dilated. There is general thickening of the mucous membrane, and towards the pyloric end this thickening is often very irregular and the surface may present a mammillated, or even a warty, appearance. The mucous membrane is reddened and hyperæmic, and as a rule shows irregular pigmented patches of a slaty-blue colour—this pigmentation being caused by changes produced in the blood in the hæmorrhagic areas. Covering the mucous membrane, there is usually an excess of viscid mucus. If the catarrhal condition is of long standing, a new-formation of connective tissue, together with atrophy of the various glandular structures, generally occurs. The overgrowth of connective tissue causes obstruction of the orifices of the ducts, and the production of small cysts. There may be hypertrophy of the muscular coat. From the stagnation and decomposition of the gastric contents, various intestinal symptoms and general toxic phenomena are produced.

ULCERATION OF THE STOMACH

1. Small multiple ulcers—called **Follicular Ulcers,** or **Hæmorrhagic Erosions** (see p. 718)—are not infrequent. They are acute and involve only the superficial mucosa, which, being damaged, undergoes necrosis and is digested, so forming the ulcer. In size they are usually only 1 or 2 mm. across, though larger ulcers, up to 1 cm. may be found. These ulcers are usually scattered irregularly over the whole mucosa and are often recognised only because of the hæmorrhage on their surface. They occur in a variety of conditions—in septicæmia, in various infections, in venous congestion, in gastritis, acute or chronic, in irritant poisoning and in phosphorus-poisoning, in the leukæmias and in purpura. In some of these conditions, the damage to the mucosa is the primary lesion, in others the hæmorrhage is primary and the ulceration follows. With the removal of the cause, these lesions tend to heal rapidly and leave no trace. It is possible they may form the starting-point of the common " peptic " ulcer. Such erosions may cause no symptoms, or may give rise to hæmorrhage and hæmatemesis.

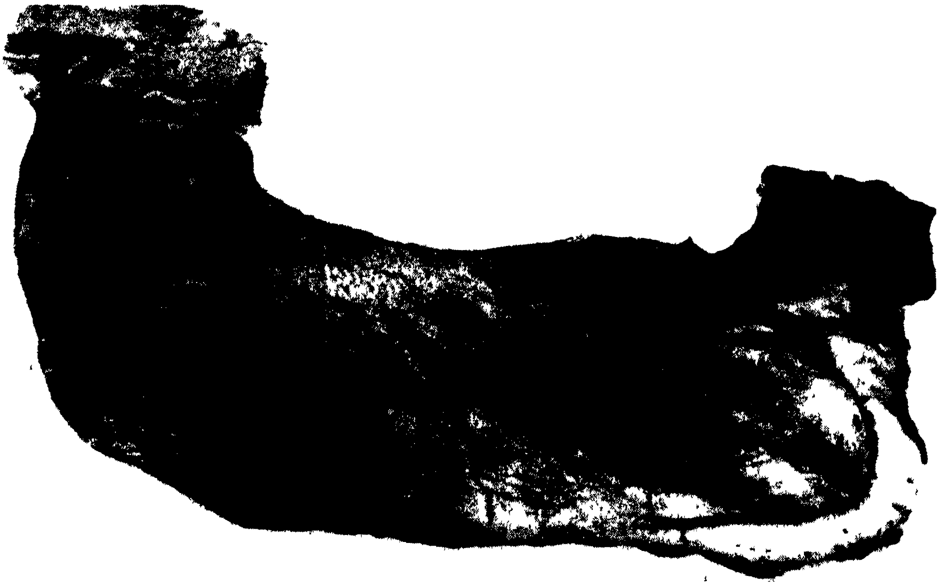

FIG. 394. Hæmorrhagic erosions in stomach (*see* pp. 718 and 719).

2. **Peptic Ulcer** (*Syn.* Gastric—and Duodenal—Ulcer, Round or Oval Ulcer, Simple Ulcer). This type of ulcer may occur in the stomach, the first part of the duodenum, in the jejunum following a gastro-jejunostomy, and occasionally in the lower end of the œsophagus immediately adjacent to the cardiac opening, *i.e.*, it occurs wherever the mucosa is exposed to the acid gastric juice. The ulcers are of uniform type in all, and one description will, therefore, serve for all, though their distribution and size may vary in the different sites. The ulcer may be acute, subacute, or chronic. The commonest form recognised clinically is the chronic. Acute, and indeed also the chronic varieties, may be found at post-mortem with no history of any clinical symptoms referable to them.

The **Acute Ulcer** may be single or multiple, and may be situated in the stomach at some point near the greater or lesser curvatures. A similar form of ulcer may occur at the lower end of the œsophagus, and in the first part of the duodenum. Their natural tendency is to heal with little or no scar, but, more rarely, they penetrate through the submucosa and muscular coat and may perforate (Figs. 395–6). Such so-called "acute" perforating ulcers, according to Matthew J. Stewart, are often better described as "subacute." Their maximum area is in the mucosa, from which the ulcers shelve into and penetrate through the muscle. There is imperfect reparative reaction in the walls of these subacute types. Such ulcers may become chronic.

The **Chronic Ulcer** may be a continuation of the acute form, but usually it arises more insidiously. Generally it is a single ulcer, but occasionally two, rarely more, are present simultaneously, though scars of previously-healed ulcers may be found.

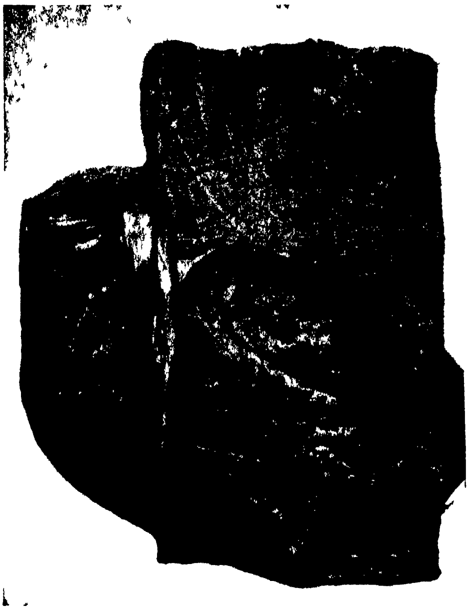

FIG. 395. *Peptic Ulcer of Stomach.* Showing the terraced appearance and oval shape. There is perforation into the splenic vein. A rod is placed in the vein.

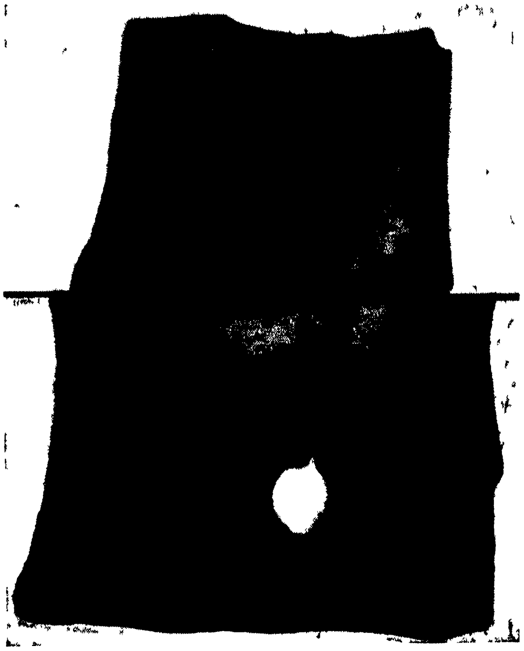

FIG. 396. *Peptic Ulcer of Stomach*—showing oval shape, shelving edge and large perforation. Above is a portion of diaphragm against which the ulcer lay. It shows an oval impression corresponding to the ulcer, and recent fibrinous exudate.

Age and Sex. Peptic ulcers are rare in childhood. They are common at any age-period from twenty years onwards. The sex-incidence as given by clinical findings varies considerably, but, from postmortem-room pathological data, A. F. Hurst and M. J. Stewart [1] (1929) put the incidence as follows :—

Type of Ulcer :—	Ratio of :— Males	to	Females.
Acute gastric	1·5	:	1
Acute duodenal	2·6	:	1
Chronic gastric	0·8	:	1
Chronic duodenal	3·5	:	1

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[1] Hurst and Stewart's "Gastric and Duodenal Ulcer," London, 1929, p. 31.

Distribution and Size. In the **stomach,** the commonest site is on the lesser curvature towards the pyloric end, and in decreasing frequency these ulcers are found in the pyloric canal, the cardiac end, and the greater curvature. They may be rounded, oval, or narrow and linear in shape, and vary greatly in size, measuring from a half to two inches or even more in their longest diameter. They may bestride the lesser curvature, or two ulcers may be directly opposite each other ("kissing ulcers"). In the **duodenum,** they occur in the commencement of the first part, especially the "duodenal cap." The ulcer may be on the anterior or posterior aspect of this part, or may bestride it, or one ulcer may be on each aspect—as in the case of the stomach.

Characters of the Ulcer. As stated, the size and shape vary, but the main characters are similar, whether the ulcer is gastric or duodenal. The **depth** to which the ulcer penetrates varies ; it may not extend beyond the mucosa, or it may involve the muscular layers and even the peritoneal coat. The edge of the ulcer is abrupt, sometimes overhung by the mucosa, its walls and floor are smooth and formed of scar-tissue which radiates out into the adjacent muscular coat. Covering this scar-tissue on its inner aspect is a thin layer of granulation-tissue with a superficial coating of necrotic debris. Inflammatory cells are often scanty in the wall, but lymphocytes and eosinophil leucocytes may be present in varying numbers. In the base of the ulcer may be seen nerve-fibres, eroded or involved in the scar-tissue ; and, from the erosion of blood-vessels, hæmorrhage results (Figs. 397–9). In an ulcer of the posterior wall of the stomach, adhesions to the pancreas, and erosion through these into that organ, may occur (Figs. 397–8). The floor of the ulcer will then consist of an admixture of pancreatic and scar-tissue. In a chronic ulcer, there is frequently well-marked endarteritis of the vessels in its base—and this may be an accessory factor in causing delay in the healing process.

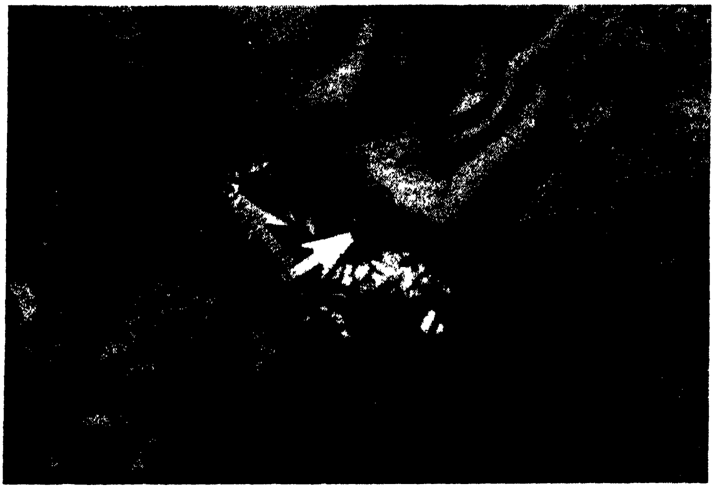


FIG. 397. Chronic peptic ulcer of stomach—showing abrupt edges and irregular base formed of pancreas. The arrows in base indicate two eroded arteries.

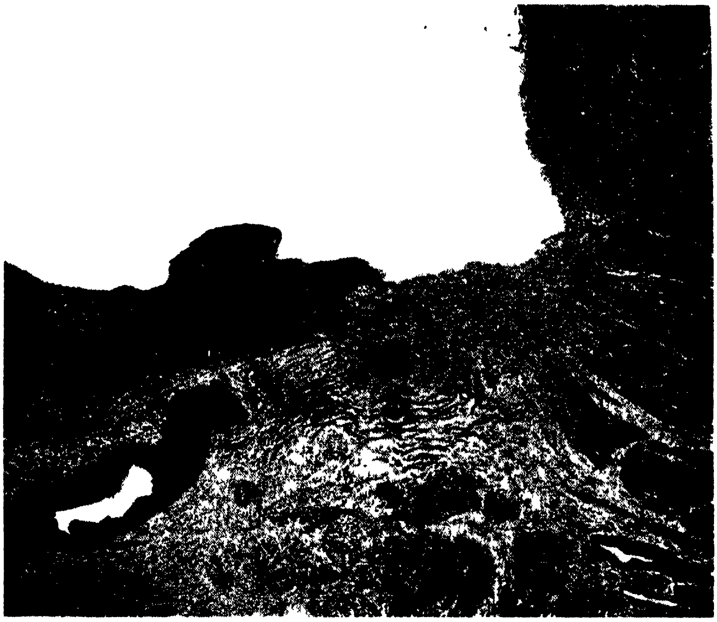


FIG. 398. Chronic peptic ulcer of stomach. The ulcer has extended through the muscle to the pancreas—seen towards middle of lower margin. The edge, to right, is formed of mucosa and scar-tissue extending into the muscle-layers. The base is composed of dense fibrous tissue in which an eroded and bleeding artery is seen to the left. × 5.

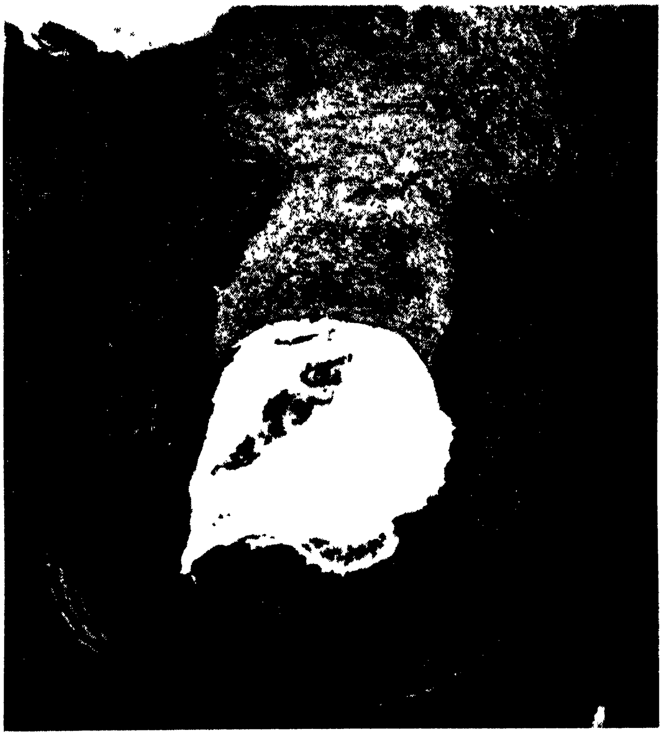


FIG. 399. Artery in base of peptic ulcer of stomach. The wall of the artery has been eroded and the gap is filled with granulation-tissue—which gave way, with resulting hæmorrhage. × 30.

Effects of the Ulcer :—

(*a*) **Hæmorrhage.** Erosion into one of the branches of the coronary or other vessels of the stomach or into the splenic vein may take place ; and the eroded vessel is often seen as a small knob-like projection in the base of the ulcer. Before actual rupture occurs, the erosion leads sometimes to weakening of the vessel-wall and aneurysmal dilatation. Such hæmorrhage may prove fatal. Analogous results follow the extension of an ulcer into the pancreas, the splenic artery or vein being involved (Fig. 395). Clinically, hæmatemesis is a common symptom of gastric ulcer ; or, if bleeding be less, melæna only may occur, or merely " occult blood " be detectable in the fæces. It is commoner in duodenal ulcer than in gastric ulcer to find melæna or " occult blood."

(*b*) **Perforation** is of more frequent occurrence in ulcers of the duodenum than in those of the stomach, and where, in the latter, rupture does take place, the ulcer is situated as a rule on the anterior wall. Often the wall of the ulcerated stomach becomes adherent to the liver or the pancreas, or less commonly to the spleen, diaphragm, colon, or abdominal wall, and thus rupture into the general peritoneal cavity is prevented. After adhesions have been formed, the ulcer may burrow into the various organs or tissues to which it is adherent, the eroded pancreatic or liver-tissue, etc., coming in this way to form the floor of the ulcer. The cavities thus produced sometimes become the sites of septic infection, and acute septicæmia may result. Perforation into the pleural cavity, into the lung or a bronchus, or into the pericardium is sometimes a sequel. Perforation occurs usually towards one side of the base of the ulcer and the opening is much smaller than the general size of the ulcer. Where adhesions are not present, or where they are slight, perforation may result in general peritonitis.

(*c*) **Stricture.** The ulcer, when situated at or near the pylorus, frequently leads to stricture, with partial, or sometimes almost complete, obstruction. Dilatation of the stomach, with all its effects, follows. When further from the pylorus, such constriction may produce the condition known as hour-glass contraction of the stomach (p. 716 and Fig. 393, p. 717). Peristalsis is delayed, dilatation and perhaps a considerable degree of hypertrophy of the muscular wall of the stomach above the constriction take place, and other ulcers may form above the constriction.

(*d*) **Healing of the ulcer** is usual, flat cicatrices being produced which may lead to considerable contraction and puckering of the surrounding stomach-wall. In the granulation-tissue at the base of such ulcers, numerous eosinophil cells are sometimes found. If the ulcer is near the pyloric ring, the cicatricial contraction may, as already mentioned, lead to the production of stenosis.

(*e*) **Carcinoma.** There is much difference of opinion as to the frequency of the occurrence of malignancy as a sequel in chronic gastric ulcer. It is probable that confusion has sometimes arisen owing to reparative proliferative changes in the epithelium at the edge of chronic ulcers being mistaken for neoplastic growth of the epithelium. That cancer is an infrequent sequel of a chronic ulcer is shown by the extensive observations of M. J. Stewart (1931) on post-mortem and biopsy material. He found only about 6 per cent. of chronic ulcers showing malignant change. The usual sites of occurrence of chronic ulcer and of gastric carcinoma are not identical, the latter being commoner at the pylorus, and ulcer more frequent on the lesser curvature a little way from the pylorus. It must, however, be remembered that ulceration is a common happening in any carcinoma, the ulceration being due to necrosis and sloughing in the malignant area.

(*f*) **Functional Effects.** **Pain** is perhaps the commonest clinical feature in gastric and duodenal ulceration. Such pain is usually relieved by food and the administration of alkali and is due mainly to the acid content, which is diluted or neutralised respectively by these additions. The pain itself is due to spasm of the muscle. **Hyperacidity** is a practically constant feature. It may precede and be a factor in the initiation of ulceration, and may be maintained by the ulceration—a vicious circle. In old-standing cases with obstruction and dilatation, the gastric secretion may be diminished, but there may be abnormal production of organic acids from retained food and bacterial decomposition. **Peristaltic movement** is often increased.

Ætiology. Experimentally, many attempts have been made to produce gastric ulceration, and successful results have been attained as regards the production of acute ulceration, which usually healed rapidly. These lesions correspond to the various acute "erosions" already mentioned, rather than to the typical "peptic" ulcer.

That the ulcerative process both in gastric and in duodenal ulceration is related to inadequately neutralised acid juice is borne out by experiments designed to upset the normal mechanisms. Thus Mann and Williamson experimentally replaced the duodenum by a loop of jejunum and found that typical chronic ulcers developed in this loop. Similar ulcers are sometimes seen as a sequel of gastro-jejunostomy in the human patient (p. 742). and have been produced in the duodenum in dogs by experimental removal of the bile- and pancreatic ducts from their normal point of entry. Florey and Harding (1933), studying the secretion in the duodenum, found that it was rich in bicarbonate, which they suggest is the normal factor in neutralising the acid gastric juice arriving there ; failure or deficiency of such secretion may thus be an important factor in the causation of duodenal ulceration. That gastric juice alone may initiate an ulcer is suggested by an experiment by Matthews and Dragstedt, in which a chronic ulcer developed in an artificially isolated sac of stomach. Chronic ulceration has also followed irradiation of the stomach in animals.

In man, it is possible that many factors are at work to initiate the ulcer. If, as Konjetzny postulates, ulceration is preceded by gastritis, the resulting irritation and spasm would allow the acid factor to operate and interfere with healing. Bacterial infection is regarded by some as the starting-point : vascular spasm, thrombosis, or infarction, by others. With regard to the first part of the duodenum, Wilkie of Edinburgh has shown that the vascular supply is somewhat precarious, and interference with this from arteriosclerosis, thrombosis, pressure or kinking, may well be a factor in lowering the vitality of the mucosa where it is most exposed to the acid juice. An apparently hereditary predisposition to the occurrence of ulceration may perhaps be related to some such vascular variation.

Whatever be the initial cause of the ulceration, the delay in healing, or chronicity, is due to the effect of the acid gastric juice, as is borne out by *the fact that healing is encouraged by allowing rest to the stomach—by regulation of diet—and protecting it from the irritation of the acid gastric juice by suitable treatment with alkalies. Rest and protection from irritation are two factors essential to healing in any part of the body.*

The process of healing may be delayed or prevented by the degree of destruction and the amount of scar-tissue already present, and by associated vascular changes such as endarteritis.

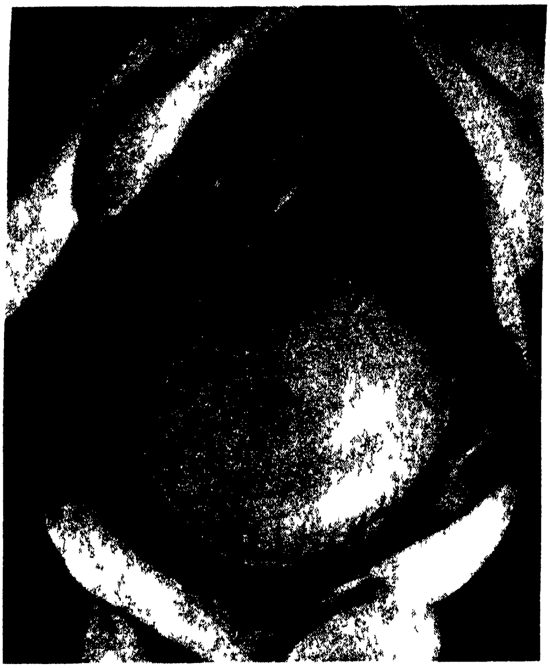


FIG. 400. Dilatation of the stomach resulting from gradual occlusion of the pylorus by a slow-growing carcinoma. The greatly-dilated stomach is seen to extend downwards almost to the pubis.

Clinically, peptic ulceration is often associated with "nervous" disturbances—anxiety, worry, etc. These factors may act by increasing the gastric, or inhibiting the duodenal, secretion.

DILATATION AND HYPERTROPHY:--

These generally result from obstruction to the passage of food through the pylorus ; but dilatation may result also from accumulation of gases derived from putrefaction of the stomach-contents caused by bacteria—a phenomenon frequently associated with chronic gastritis—the inflammatory condition of the stomach no doubt aiding, by weakening the muscular wall and lessening its power of peristalsis.

Acute dilatation is said to occur after a severe mental shock. This so-called "idiopathic dilatation" is due to an interference with the nervous mechanism of the organ. An important and dangerous form of such acute dilatation is sometimes found following operations, especially on the abdominal

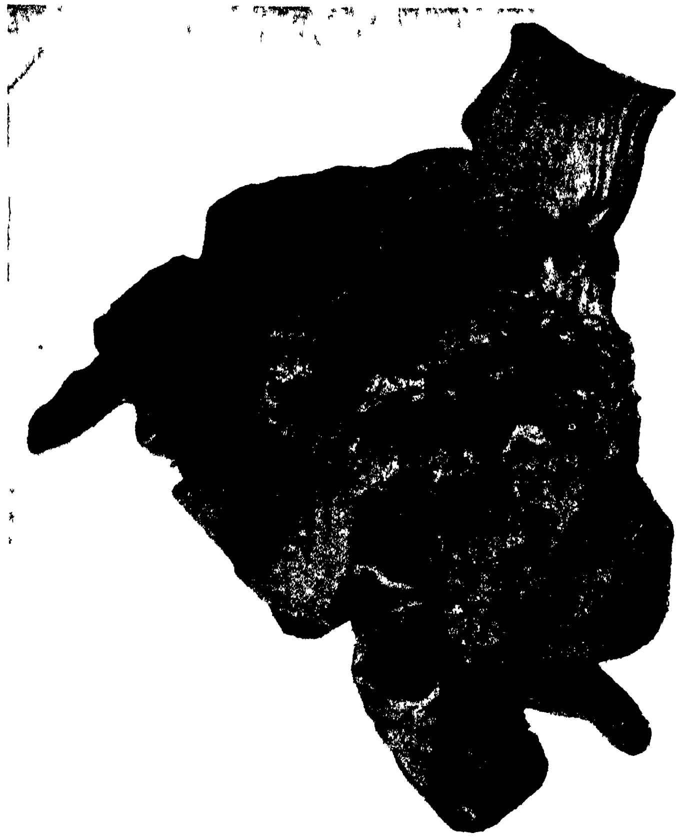


FIG. 401. *Encephaloid or Soft Cancer* at the cardiac end of the stomach immediately below the opening of the œsophagus.

cavity. As a result of the dilatation, the greater curvature and perhaps also the pylorus, are displaced downwards.

Chronic Dilatation. The muscular wall of the stomach, in cases in which the pylorus is chronically obstructed, undergoes **hypertrophy**, especially at the pyloric end, and this hypertrophy may involve the whole organ and even also the œsophagus, particularly in infants with congenital hypertrophic pyloric stenosis (p. 716). If the obstruction is not relieved, the stomach will eventually become atonic and dilated (Fig. 400).

ATROPHY AND DEGENERATIONS :—

Atrophy of the stomach-wall may occur in old age, starvation, and wasting diseases, or where there is obstruction in the œsophagus or at its cardiac opening. It may occur in carcinoma of the stomach and in Addisonian anæmia (*see below*). Such atrophy involves the gastric glands as well as the supporting tissue and muscle.

Achlorhydria, or absence of the normal hydrochloric acid, may occur as a result of atrophy of the gastric mucosa, but it may also be present apart from that condition, and, indeed, may be a congenital defect, seen sometimes in several members of a family. It appears as the result of dietary deficiency, particularly of the vitamin-B_2 complex, and is sometimes associated with hyperthyroidism. Absence, or deficiency, of acid may be the only abnormality, but more usually this is associated with or followed by defective secretion of pepsin (**achylia**), and finally by disappearance of the "intrinsic factor" **hæmopoietin,** necessary for the maturation of the red blood-cells in the marrow, thus leading to the production of a "**macrocytic**" anæmia (*see under* Anæmia, p. 647 *et seq.*). Exceptionally, the "intrinsic factor" may be absent even with secretion of acid. Achlorhydria may lead to defective assimilation of iron and so give rise to a "**microcytic**" anæmia (p. 644). Achlorhydria is the usual finding in the gastric juice in carcinoma of the stomach; and the occurrence of a "macrocytic" anæmia is not unusual in such cases. W. Jacobson (1939) has recently shown that Castle's "intrinsic hæmopoietic factor" (p. 648) is probably produced in the **argentaffine** (or **argyrophil**) **cells** of the gastric, and to a lesser degree by those of the intestinal, mucous membrane.

Fatty degeneration of the cells of the glands and gland-tubules, and of the vascular endothelium, results from the action, acute or chronic, of either organic or inorganic poisonous substances. This condition is seen especially in phosphorus-poisoning, in septicæmia, and similar conditions.

Amyloid degeneration is rarely found in the blood-vessels of the mucous and submucous coats of the stomach (p. 211).

Tuberculosis and **Syphilis** (pp. 71 and 82–3, Granulomata).

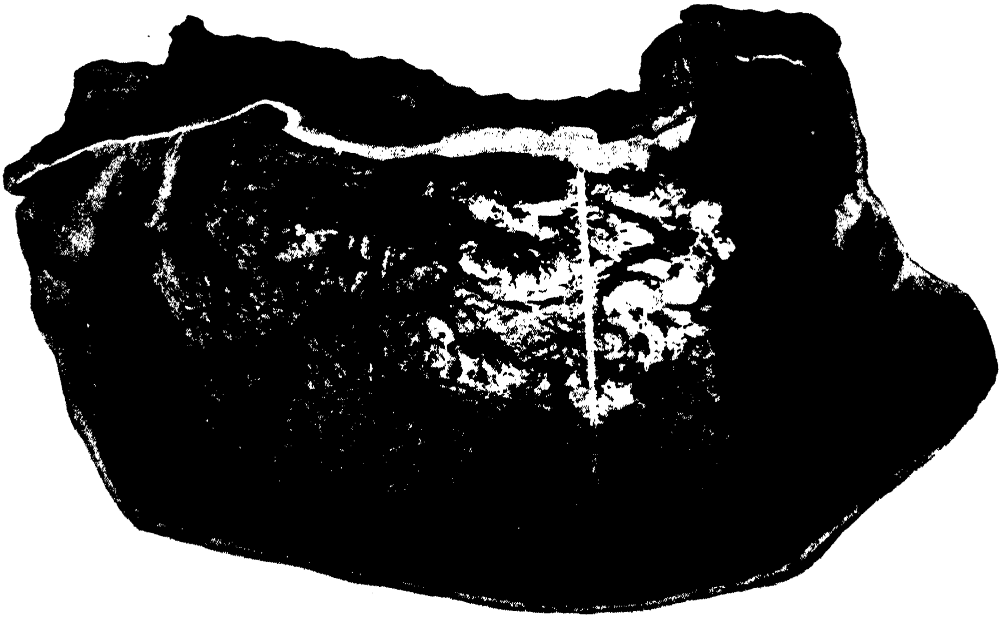
TUMOURS :—

Fibromas, myomas, lipomas, and simple adenomas are occasionally found. Sarcomas are rare, and, when present, are generally of the small round-celled type, especially lymphosarcomas.

Carcinoma is the commonest and most important tumour of the stomach. It occurs generally in the later periods of life, and is commoner in the male than in the female. The most frequent sites are the pyloric end of the stomach and the lesser curvature, though it may develop at the cardiac orifice or at any area in the body of the organ. About 60 per cent. are found at the pylorus or in its vicinity, 20 per cent. at or near the lesser curvature, 10 per cent. at the cardiac orifice, and 10 per cent. in other parts of the stomach-wall.

The tumours are usually **adenomatous** in type, and frequently show "**colloid**" or **mucinoid degeneration** (pp. 340 and 349). Those at or near the pylorus tend to grow slowly, and, during their growth, a considerable amount of fibrous tissue is formed, with only a moderate degree of cellular proliferation, giving a tumour of the **scirrhous** type (p. 344). In some of these, the fibrous tissue is so abundant that the malignant cells are difficult to find, and it may be that some so-called fibrous strictures are in reality carcinomas in which the fibrous overgrowth has prevailed. Fibrous strictures of the pylorus due to chronic inflammatory changes occur, and cases are not infrequently reported in which a large "tumour," supposed to be "cancer," had been previously present and had disappeared after gastro-enterostomy. This disappearance is taken as proof that the mass was inflammatory, although it is just possible that some of these

FIG. 402. *Carcinoma of pylorus*, showing infiltration through wall of stomach and ulceration of inner aspect of tumour.



. 403. *Carcinoma of the Stomach.* A large fungating mass growing from the anterior wall and showing extensive ulceration.

cases may have been carcinomas in which fibrous overgrowth predominated over that of the cancer-cells. Carcinomas of the body of the organ and of the lesser curvature grow more rapidly, and may form irregular, fungating, cauliflower-like excrescences, projecting into the cavity. These tumours are highly cellular, and exhibit the type of malignant adenoma or sometimes encephaloid cancer.

Effects on the Stomach. Carcinoma at the pyloric orifice causes a ring-like infiltration of the mucous and submucous tissues, and thus produces a stenosis of the orifice which leads to dilatation and muscular hypertrophy of the organ, with stagnation of food and consequent fermentation, the latter being aided by alterations in the normal secretions, especially deficiency or absence of hydrochloric acid, and the multiplication of various bacteria, yeasts and torulæ.

Ulceration of the inner surface of the tumour, and hæmorrhage, are usually later manifestations. Carcinoma of the body of the stomach or at the cardiac orifice frequently becomes ulcerated, and hæmorrhage is a common sign of the disease, showing clinically as hæmatemesis, melæna, or "occult blood." **Achlorhydria,** generally accompanied by **achylia,** is the usual finding in gastric carcinoma and later, probably from involvement of the argentaffine cells, a macrocytic type of anæmia may supervene (pp. 624 and 648). Owing to interference with the peristaltic movements of the stomach-wall, stasis and loss of appetite are present ; and vomiting may occur either from pyloric obstruction or from the irritation of the tumour.

Method of Extension of Carcinomas of the Stomach. The extension of the tumour takes place by an infiltration of the mucous and submucous coats, leading to general thickening of a considerable portion of the stomach-wall, or to the formation of irregular, projecting, fungating masses, which are highly vascular and easily damaged, and in which ulceration is extremely common. The infiltration may spread into the muscular and peritoneal coats, and, in rare instances, perforation may result. Occasionally, especially in the case of slow-growing tumours, the infiltrated and thickened stomach-wall undergoes great contraction, and may even come to form a narrow, thick-walled tube, somewhat resembling a piece of thickened intestine—the so-called "leather-bottle stomach" (*see opposite* –Plastic Linitis).

The cells of carcinomas of the stomach frequently produce mucin which distends the cells, and gives them a "signet-ring" appearance. Peritoneal metastases from this type are common, and, in the female, bilateral ovarian metastases, known as **Krukenberg's tumours** (pp. 349 and 929–30), may be produced. Secondary growths are common in the liver and in the peritoneum ; and the lymph-nodes in connection with the stomach are usually involved. Metastasis in the mediastinal nodes may occur, and it is not uncommon to find enlarged cancerous nodes at the root of the neck, particularly on the left side, in such cases. Occasionally, widespread secondary growths in bones, especially in the bodies of the vertebræ, but sometimes in practically every bone in the body, may supervene and may, in some eight per cent. of cases in which such metastasis is suspected, be confirmed by the finding of malignant cells in sternal-puncture biopsy-specimens (pp. 605–6).

"Plastic Linitis." **(Cirrhosis of Stomach : Fibromatosis of Stomach).** This condition, formerly thought to be chronic inflammatory in nature, is now known to be a diffusely infiltrating scirrhous carcinoma. Its cells are usually of a small poorly differentiated type seldom with any indication of glandular organisation. The pyloric region is usually the site of origin, but the lesion progresses slowly, and eventually the entire stomach and much of the peritoneum may be involved. The stomach-wall becomes thick and rigid and the lumen greatly contracted. Microscopically, the carcinoma-cells are found scattered individually and in single-file columns between fibres of muscle and connective tissue.

SECTION III

DISEASES OF THE INTESTINES

Congenital Malformations :—

From a fault of development, part of the large or of the small intestine may be absent. This is seen especially in the rectum, the lower part—the proctodæum—having failed to unite with the portion above, so that the condition of **imperforate anus** is produced. In some cases, the rectum has in the male been found to open into the urethra, and in the female into the navicular fossa of the vulvar cleft—or to end in a fibrous cord at the base of the prostate or in connection with the vagina. There may, in other instances, be defective development, with congenital narrowness, or sometimes with complete occlusion—atresia—of the small intestine, especially in the duodenum or the lower end of the ileum close to the ileo-cæcal valve ; or there may be stenosis at the junction of the pelvic colon with the rectum.

The commonest malformation is a **Meckel's diverticulum**. This varies from a slight rounded hollow bulge to a long tube-like pouch, which is most commonly some 2 or 3 inches long, and may be continued by a fibrous cord. In infants it is found at from 12 to 18 inches, and in adults at from 2 to 3 feet, above the ileo-cæcal valve. It possesses the same structure as the intestine, has usually a somewhat narrower calibre, and is in direct communication with the lumen of the bowel. This diverticulum arises from the imperfect closure of the vitello-intestinal duct, and is sometimes connected with the umbilicus, where, if not completely closed, it gives rise to a fæcal fistula. If the lumen in some part of its course becomes shut off, the dilatation which follows as a result of the accumulation of secretion in this closed sac may give rise to the formation of a cyst—the so-called **enterocystoma.** Aberrant pancreatic glandular tissue and gastric mucosa are frequently found in a Meckel's diverticulum. Typical peptic ulcer, leading even to perforation, may occur in areas of such ectopic gastric mucosa.

Diverticula are found frequently *post mortem* without any antecedent clinical symptoms. The term **Diverticulosis** is used to denote their presence, whilst **Diverticulitis** is applied to inflammatory change in such diverticula.

Some diverticula may occur as congenital malformations, but usually they are seen as acquired lesions and only in the adult, especially in elderly people.

In the **duodenum** and commencement of the jejunum, they are uncommon and are usually in the form of irregular dilatations of the lumen. They may be saccular and press upon and obstruct the pancreatic duct and common bile-duct. Infection is rare here, though we have seen a case of fatal perforation of such a sac from a piece of bone impacted in it. Along the **jejunum and ileum,** multiple diverticula may occur between the layers of the mesentery along the line of its attachment at the point of entry of the mesenteric vessels (Fig. 404). These diverticula consist usually of all coats of the intestine, though the muscular layers are often thinned or may be absent. **Diverticulitis** is rare in this situation, its commonest site being the **colon** (Figs. 405 and 406), of which all portions in varying degree may be affected, though the sigmoid is most frequently involved. The sacculations occur between the longitudinal bands of muscle and frequently consist of mucosa and submucosa only—a form of herniation through the muscle-coat (Fig. 406). In the colon, fæcal matter tends to accumulate in the diverticula, and **diverticulitis** is common. The inflammatory change may extend to the surrounding tissues, forming an indurated mass clinically suggestive of a carcinoma. Perforation, with local or general peritonitis, may occur, or neighbouring coils of intestine may be eroded. We have seen a case where an inflamed diverticulum of the sigmoid became adherent to the bladder, with perforation into it and discharge of fæcal matter and pus *per urethram*.

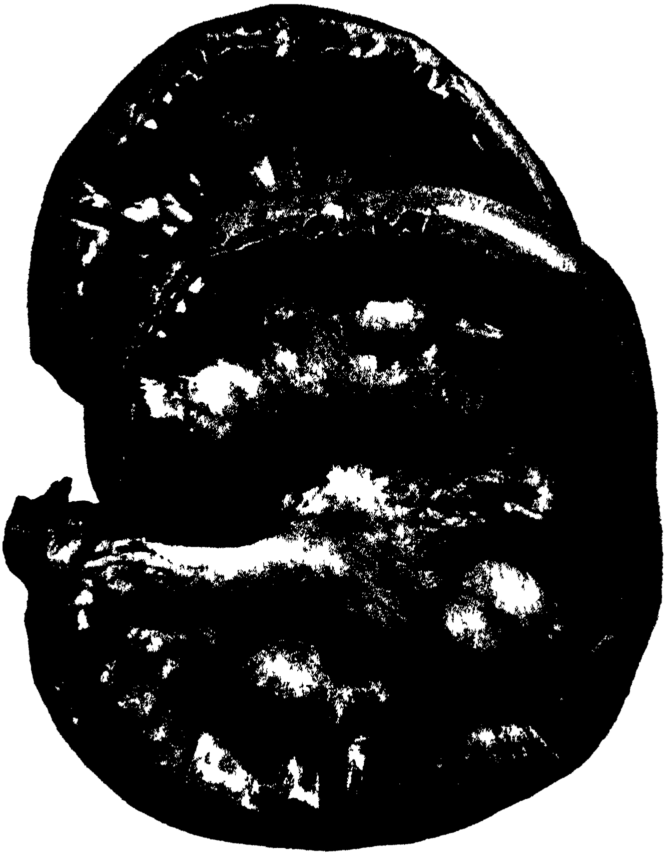


FIG. 404. Multiple diverticula of the small intestine.

In some diverticula of duodenum or jejunum, islets of **aberrant pancreas** are found at their tips. Such islets, and diverticula if also present, occur usually on the side of the gut farthest from the mesentery.

By X-ray examination after a barium-meal, diverticula show up well. Symptoms, if any, are usually those of obstruction. Constipation may occur

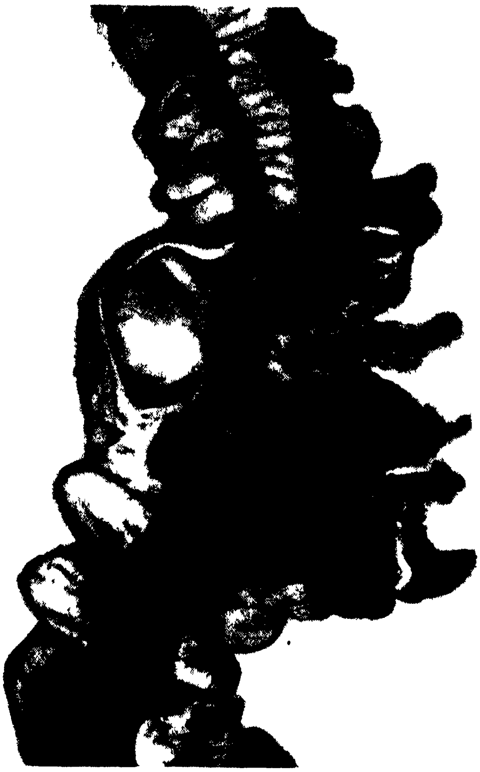


Fig. 405. Diverticulosis of colon. A portion is opened to show numerous diverticula.

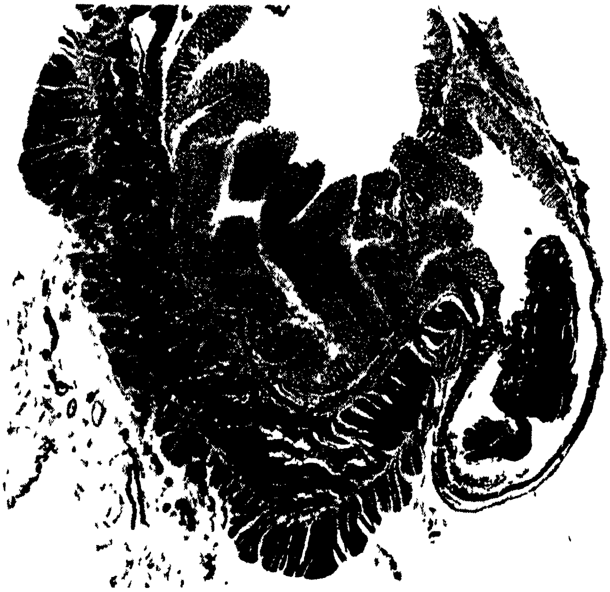


Fig. 406 Diverticulum of colon. A section through the colon showing one diverticulum, to right, with absence of muscle in its wall and fæcal content in its lumen. × 6.

and may be a factor in developing the diverticula at vulnerable points along the intestinal tract.

Similar diverticula occur in the appendix.

Transposition. Occasionally, transposition of the intestines occurs without transposition of the other viscera. Usually, however, it forms part of a more generalised transposition (Fig. 251, p. 447).

Dilatation :—

In "Hirschsprung's disease," **megacolon** or **megalocolon,** great dilatation of the pelvic colon and, in some cases, also of the iliac and descending portions of the colon, or even of the whole colon, occurs, along with hypertrophy of the muscle-fibres in the wall. In cases in which the condition has lasted for some time, considerable fibrous hyperplasia supervenes, and, if scybalous masses are retained in the dilated bowel, numerous irregular ulcers of the mucosa may arise. The condition is present in the infant and is associated with chronic constipation. It may persist to adult life when the colon may have attained an enormous size. J. R. Learmouth [1] considers that the dilatation is due to a local segmental neuro-muscular inco-ordination, with or without achalasia of the internal anal sphincter. Although there is functional obstruction, no mechanical block can be demonstrated and peristalsis may be strong, yet the enlarged colon becomes a reservoir for great fæcal accumulations. That the condition is due to some interference with nervous control (p. 1190) is supported by the satisfactory results which have followed section of the appropriate sympathetic fibres (resection of the mesially directed branches of the lumbar ganglia from the 2nd to the 4th inclusive)—which inhibit emptying of the colon (*cf.* achalasia of œsophagus, p. 713). Acute dilatation or distension of the intestine—"**paralytic ileus**" [2] (pp. 736 and 760)—is a common manifestation in cases of inflammatory conditions in the abdomen, *e.g.*, peritonitis. Dilatation of a more or less uniform character may result from prolonged constipation, or from unknown causes, and is sometimes extreme in degree.

HERNIA :—

This term has a wide application, but, in connection with the abdominal cavity, it is generally taken as applying to a protrusion of some part of the intestine, the omentum, or other portion of the abdominal contents, into a sac composed of a diverticulum or prolongation of the peritoneum. The two commonest forms are **inguinal** and **femoral** hernias. The former is a protrusion, usually of some portion of the intestine, of the omentum, or of both of these, through the external inguinal ring, the contents descending through the inguinal canal: or a protrusion directly forwards through the internal inguinal ring under the skin of the abdomen. Femoral hernias are commonest in women, and consist of a protrusion of some part of the abdominal contents through the femoral ring, the hernia showing itself at the antero-internal aspect of the thigh, at the position of the saphenous opening. Hernias at the sciatic notch and at the obturator foramen, or into the perineum or the vagina, at the umbilicus, at the sites of surgical and other wounds, etc., need only be mentioned. Full descriptions of these will be found in text-books of Surgery.

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[1] *Brit. Med. Jour.*, 1937, ii, 154.

[2] "Ileus," Greek εἰλέος or ἰλεός, *eileos* or *ileos*, "a grievous disease of the intestine" (Liddell and Scott)—through Latin *ileus volvulus,* from εἰλέω or εἴλω, *eileō* or *eilō,* to roll or pack up tightly, to revolve or twist. "Ileus, a colic caused by a stoppage in the intestines": "Ileac passion, a colic of a dangerous type, in which the peristaltic action of the small intestines is inverted" (Nuttall's "Standard Dictionary"). "Paralytic ileus" is, therefore, a contradiction in terms, and it is well to understand the exact meaning of the word "ileus" *if* it is so used here.

Congenital forms occur (*a*) at the **umbilicus** ; (*b*) in the **inguinal region.** In the former, the sac is formed by an unobliterated umbilical process. In the inguinal region, in the male, the sac is composed of a persisting **processus vaginalis,** so that abdominal contents can descend along the inguinal canal to the scrotum. In the female, the analogous canal or processus vaginalis, the "**canal of Nuck,**" occasionally remains patent and so allows of the production of a hernia into the labium majus.

Ætiology. Hernias may be **congenital** or **acquired.** In the production of **acquired hernia,** two important factors come into play, viz., undue pressure: and weakness, or imperfect or arrested development, of the supporting structures. Hernias resulting from undue pressure arise most commonly as a consequence of severe muscular efforts such as are involved in lifting heavy weights, straining at stool, or constant coughing. The contraction of the muscles of the abdominal wall exerts considerable pressure on the contents of the abdomen, the wall gives way especially at unsupported parts, and a varying volume of the contents is protruded.

Pathological Anatomy. In the congenital forms, portions of the intestines or other contents project into the pre-existent tubes or sacs of peritoneum already mentioned. In the acquired forms of hernia, the sac is composed of stretched peritoneum. In rare cases, this may rupture or disappear, and no definite sac be present.

The sac usually acquires, by a chronic inflammatory process, adhesions to the structures amongst which it is protruded, and sometimes to its contents.

Contents of the Sac. The parts most commonly protruded are, as already noted, some portion of the intestines and the omentum, but the sac may contain any part of the abdominal contents. The neck of the hernial protrusion is usually constricted, sometimes sufficiently to cause interference with the blood-supply to the contents—"**strangulation**" (*see* p. 736). The immediate effect is obstruction of the veins, leading to the production of congestion and œdema. The protruded portion may become dark in colour. Later, arterial obstruction may also take place, and this, if sufficiently complete, leads to the occurrence of necrosis and gangrene (Fig. 407, p. 736). Obstruction to the onward passage of the contents of the bowel is another important consequence.

Internal Hernias are generally protrusions of parts of the abdominal contents into pre-existing pouches, or through normal or abnormal apertures. The two most important of these are :—

1. **Diaphragmatic hernia.** The true diaphragmatic hernia is a protrusion into the chest of some of the abdominal contents, through one of the normal apertures, or through a part of the diaphragm which, by reason of defective development is absent, has given way, or has been ruptured by mechanical injury. The congenital form is commonest on the left side. The contents

of the hernial sac are most usually intestine, spleen, liver, or stomach. More rarely, herniation of part of the thoracic contents, for example the heart, may take place downwards into the abdomen.

2. **Retroperitoneal hernia** consists of a protrusion into one of the pre-existing peritoneal pouches, which generally lie behind the peritoneum from which they are offshoots. The most important of these pouches is the paraduodenal fossa, which lies behind the last part of the duodenum and arises at the junction of the duodenum and jejunum.

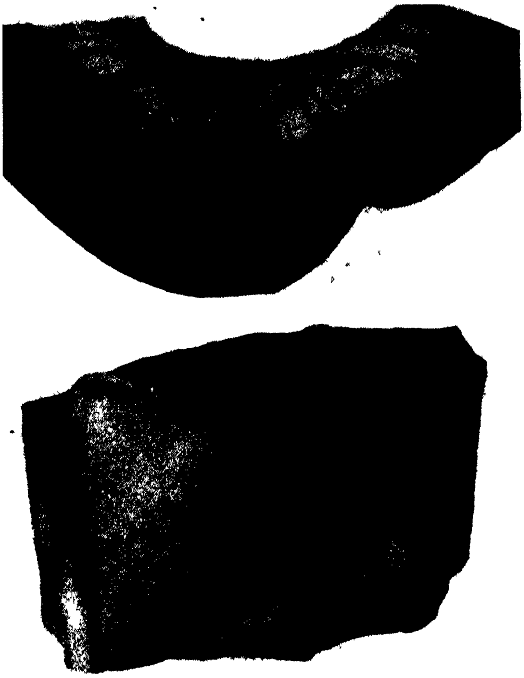

FIG. 407. Strangulated inguinal hernia. Above is shown the portion of ileum which was impacted and which had become hæmorrhagic and gangrenous. Below is the opening of the sac as seen from within the abdomen.

Post-operative hernia. Portions of intestine or omentum may find their way into stretched scars or imperfectly closed wounds resulting from operations on the abdomen.

STRANGULATION :—

Internal strangulation may be brought about by compression and obstruction of the intestine by fibrous peritoneal adhesions, by a persistent cord of a Meckel's diverticulum, by a twisting of the coils upon themselves (**volvulus**), or by the passage of a loop of bowel through an abnormal opening in the mesentery or elsewhere. Dilatation of the intestine occurs above the seat of the obstruction ; and congestion, hæmorrhage into the lumen of the bowel and perhaps into the peritoneal cavity, peritonitis, necrosis, gangrene, and perforation may result. Strangulation of the bowel in a hernial protrusion has already been described. It may result also from intussusception (*see* p. 737). However produced, strangulation may give rise to "**paralytic ileus**", so-called (p. 734), especially if peritonitis supervenes as a result of the strangulation.

VOLVULUS may affect practically any part of the more mobile portions of the bowel. It may involve even the cæcum when it possesses a mesentery; but is found most frequently in the pelvic colon. This portion of the intestine is attached by its two ends to the abdominal wall, and it sometimes twists round this attachment as an axis—the upper loop generally turning round the lower. The twisting causes obstruction, and the bowel above the constriction becomes greatly distended ; and, if the condition persists and does not rapidly lead to a fatal issue owing to acute strangulation, the muscular walls may become hypertrophied and the loop of bowel greatly dilated.

INTUSSUSCEPTION :—

This is a condition, occurring most frequently in children, in which one part of the intestine is invaginated into the lumen of the immediately adjoining part. It may occur at any part of the bowel, the most usual site being at the ileo-cæcal valve—the valve and the lower part of the ileum being carried onwards into the ascending portion of the colon. The invagination may be extreme, and the apex of the intussusception may even present at the anus. Sometimes, but much less frequently, the invagination occurs in the small intestine. In whatever situation it takes place, it is always the upper or proximal part of the bowel which is drawn into the lower or distal ; for it is by the peristalsis of the lower part, and the absence of peristalsis in the enclosed upper portion, that the invagination occurs. Once the condition has commenced, it may continue as long as the peristalsis persists, and more and more of the intestine be thus invaginated. The mesentery is carried in with the intestine, and, by dragging upon one side of the bowel, it tends to give to the latter an oblique direction. The packing-in of the intestine and the pressure on the mesenteric veins cause congestion of the bowel and, perhaps, hæmorrhage into its coats, interference with its nutrition, inflammatory changes, and even gangrene. Sloughing, with general peritonitis, may result ; or permanent adhesions may occur between the outer ensheathing part and the upper end of the included portion, and in the latter case the invaginated part may, by necrotic or gangrenous changes, become separated and be passed *per rectum*, the continuity of the bowel being restored, with the loss of this gangrenous portion.

"**Agonal intussusception.**" Invaginations in the small intestine are frequently seen at post-mortems. They are common in children, especially in intestinal cases, and are often multiple—as many as a dozen or more being not infrequently found. They are usually small, but occasionally may be two or three inches long. These show no inflammatory or congestive changes, are without adhesions and are easily undone on gentle traction. They are due probably to local interference with peristalsis during the death-agony, and are of no special pathological significance.

PROLAPSE OF THE INTESTINE :—

This is usually a prolapse of the lower part of the rectum and anal canal (**prolapsus ani**), due to a weakness of the sphincter and to constant straining. It is commonest in young children, but may occur in adults and is frequently associated with hæmorrhoids. In some cases, the mucous membrane of the lower part of the rectum alone is protruded ; whilst, in other cases, the upper, more movable part of the rectum may be invaginated into the lower part and then protruded. The exposed mucous membrane, if not immediately replaced, becomes inflamed ; and ulceration, hæmorrhage, and necrosis may subsequently result.

ATROPHY AND HYPERTROPHY :—

Atrophy of the mucous membrane of the intestine occurs in any wasting disease such as tuberculosis or cancer, or as a result of chronic inflammatory lesions, and is seen frequently in cases of Addisonian anæmia (for atrophy of the argentaffine cells in this, see pp. 648, 653 and 728) and in marasmic children. Atrophy of the various coats may occur from interference with function, and is seen sometimes as a result of starvation, or in the intestine below the site of a stricture, or even throughout the whole of the intestine in cases of cancer of the œsophagus or of the cardiac or pyloric orifices of the stomach. The atrophy is sometimes masked by a general œdematous condition of the intestinal mucous membrane.

Hypertrophy of the **muscular coat** occurs above the sites of strictures or in cases of chronic obstruction produced by other causes, and is usually associated with dilatation. **Congenital hypertrophies** of the various sphincteric areas of the alimentary canal are described on pp. 713, 716–17 and 734.

Hypertrophy of the **lymphoid tissue** is a constant feature in those cases which have been described under the term "lymphatism" (p. 686), the solitary follicles standing out as little bead-like swellings, and the Peyer's patches (aggregated lymphatic nodules) often showing even more marked swelling than that seen in typhoid fever before ulceration (p. 751–4 and Fig. 419).

DEGENERATIONS :—

The most important of these is **amyloid** degeneration (p. 211), which is usually associated with amyloid changes in the liver, kidneys, and spleen in tuberculous disease or in syphilis. It affects the arteries and capillaries of the mucosa and submucosa, and is seen especially in the vessels of the villi. The intestine looks smooth and pale-pink or greyish in colour, but the condition is best detected by the application of iodine, with which the vessels show up as a mahogany-brown network. This degeneration is usually associated with chronic catarrh. Superficial erosions or ulcers may be present.

CIRCULATORY DISTURBANCES :—

(*a*) **Chronic venous congestion** is a common pathological change in the intestine. The mucous membrane becomes swollen, and assumes a dark bluish or even a slate-grey colour. Hæmorrhages in the submucous and mucous coats are frequently seen. There usually is associated catarrh, and, perhaps, œdema, the latter condition being, as a rule, most pronounced in the duodenum and upper part of the jejunum.

(*b*) **Hæmorrhage.** Petechial hæmorrhages occur in the mucous and submucous coats of the intestine in many of the infective diseases, in cases of profound anæmia, in poisoning with phosphorus, and in chronic venous congestion. Larger hæmorrhages may occur from any part of the intestinal tract secondary to malignant growths, and as the result of intense inflammatory changes in the intestine itself, especially in infective diseases in which ulceration occurs, as in typhoid fever, in dysentery, and in duodenal ulcer. Large hæmorrhages either into the lumen or into the wall of the intestine occur in purpura ("Henoch's purpura," p. 670), and, clinically, the mass may simulate intussusception with acute obstruction, giving rise to a palpable sausage-shaped mass. These hæmorrhages are accompanied by acute inflammatory changes, necrosis, gangrene, ulceration and peritonitis, often with a fatal result. In the leukæmias, hæmorrhages of varying size may occur. Obstruction of the superior mesenteric artery or some of its branches, with or without thrombosis of the corresponding vein, is a comparatively rare condition, but when it occurs, as by embolism or thrombosis, great engorgement follows, often with hæmorrhage, the area of infarction usually undergoing necrosis and gangrene, which may also follow upon the still rarer condition of thrombosis of the vein only (Figs. 408–9). Strangulation, however produced, may give rise to hæmorrhage. Clinically, such lesions are characterised by the passage of blood in the stools. The amount and appearance of such blood vary greatly according to the site and nature of the lesion. It may be fluid or clotted, bright red if fresh, or—if altered by the action of the sulphuretted hydrogen in the bowel—of a brownish-black or black colour, the condition being then known as **melæna.** It may be so small in amount as to be diagnosed only by special tests for "occult blood." Blood in the stools can also, of course, originate from some lesion such as malignant disease or simple ulcer of the stomach, or the blood may have been swallowed.

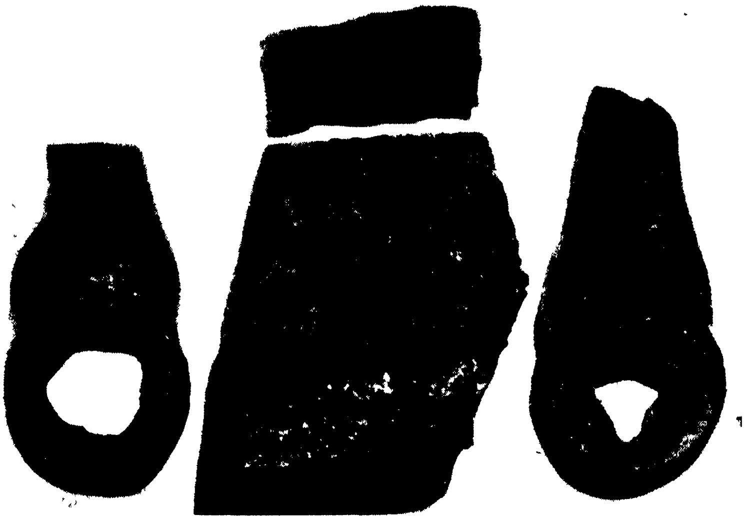

FIG. 408. *Thrombosis of superior mesenteric vein* in a woman of fifty years, in whom it caused acute intestinal obstruction. Note the "hose-pipe-like" thickening of the bowel-wall from hæmorrhage and œdema. The next figure shows microscopical details. Operation specimen : (Dr. Worster-Drought's case.) (Natural size).

Local hæmorrhage from the rectum itself results from the rupture or ulceration of **hæmorrhoids**, which are produced by varicose dilatation of the veins of the rectum and anal canal. They are found usually at the lower part of the bowel, outside or inside the sphincter ani. The main cause of their production is obstruction of the portal venous circulation, which may be brought about by such conditions as cirrhosis of the liver, repeated pregnancies, tumours in the pelvis, or chronic constipation ; but another important factor is obstruction to the systemic venous circulation. The hæmorrhoidal veins are radicles of the portal vein, do not possess valves and communicate freely with the neighbouring tributaries of the inferior vena cava. They are thus liable to become dilated when there is interference with the blood-flow in either of these great systems. In chronic constipation, the fæces become unduly solid and cause constant pressure on the ascending veins, the contraction of the rectal wall is increased in force, and this tends to constrict the apertures through which the veins pass, and the expulsive expiratory efforts, which raise the blood-pressure in the portal and systemic venous system, are prolonged. The repeated and severe distension thus induced leads to the production of permanent varicosity.

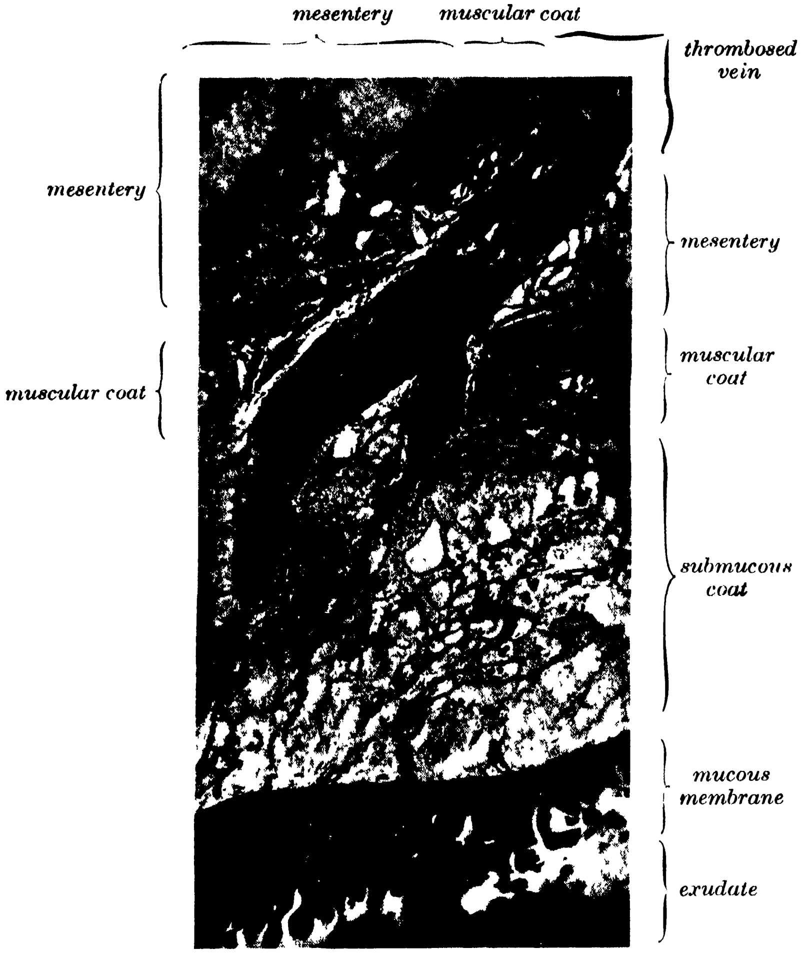

FIG. 409. *Thrombosis of superior mesenteric vein :* very low power view of section of mesentery and bowel-wall from same patient (Fig. 408). The submucous coat of the bowel is greatly swollen and œdematous, with dilated capillaries and lymphatics : the mucous membrane semi-necrotic, with fibrino-purulent exudate in the lumen. The thrombosed vein, joined by tributaries from the swollen submucous coat, is seen passing obliquely through the muscular coat up into the mesentery. Mallory's connective-tissue stain. × 20.

The hæmorrhoids may be **external** and the veins surrounding the anal margin be alone distended ; but, more commonly, **internal** and **external** piles occur together (Fig. 410). Usually, the connective tissue supporting the veins is thickened and fibrosed as a result of repeated irritation or recurrent inflammatory attacks. Most so-called " external piles " are due to the rupture of a small vein, which previously may or may not have been varicose, and are in reality small **peri-anal hæmatomas.**

FIG. 410. Hæmorrhoids. The lower portion of the rectum with anus. In the rectal mucosa are many petechial hæmorrhages. Around the anus are the hæmorrhoids, mainly of the external variety.

Internal hæmorrhoids consist primarily of dilatations of the radicles of the superior hæmorrhoidal vein and, secondly, of connective-tissue increase in the columns of Morgagni. At first, they may appear as flat, longitudinal folds of mucous membrane, but, later, they increase in size, and become more rounded and often pedunculated. The distended veins may rupture, or ulceration may take place. As they increase in size, they tend to become prolapsed through the anus. The hæmorrhoids appear as polypoid elevations of a dark-red, congested appearance. On section, these are found to consist of dilated veins, surrounded by inflammatory connective tissue as a supporting structure. Thrombosis may occur in them ; the clot may organise and the pile be reduced to a small fibrous mass ; or an infective phlebitis may be set up.

Thrombosis of Mesenteric Vessels and Infarction of the Intestine are described on pp. 739 and 178. Obstruction of the mesenteric vessels may be of the arteries, the veins, or both sets of vessels. Fig. 408, on p. 739, shows the serious results of the thrombotic obstruction of mesenteric veins without obstruction of the corresponding arteries. Figs. 290 on p. 499, and 408–9 on pp. 739–40 are from a section of the mesentery from a woman aged 50, who suffered from an attack of acute intestinal obstruction produced by the thrombosis of a large tributary of the superior mesenteric vein.

INFLAMMATION : –

The inflammatory affections of the intestine involve especially the mucous and submucous coats, and vary, both in character and in intensity, from those which show merely superficial catarrhal changes to those in which there is suppuration or extensive ulceration.

1. **Acute catarrhal enteritis** is common in children, but occurs also in adults. The causal factor is usually the ingestion of unsuitable food, or exposure to cold ; or it may occur as the result of one of the acute infective fevers. In some of the severer affections of the bowel, *e.g.*, in the summer- or autumn-diarrhœa of children, bacteria in contaminated milk and other foods play an important part. The large intestine, with the cæcum and the vermiform appendix, are common sites, but the condition occurs frequently at the lower part of the ileum, just above the ileo-cæcal valve, and may be found also in other parts of the small intestine. The congestion may be diffuse, or it

may be localised especially to the valvulæ conniventes and the tissues round the solitary lymph-follicles. The mucous membrane may, in addition, be swollen, soft, and covered wholly, or in parts, with a layer of viscid mucus. In some cases, *e.g.*, in the catarrh seen in scarlet fever, measles, diphtheria, etc., there is considerable swelling of the solitary follicles, especially towards the lower part of the small intestine ; whilst, in other cases, small follicular ulcers, from one-sixth to one-eighth of an inch in diameter, develop. These ulcers may heal and leave small scars.

2. **Chronic catarrh** is commonest in the large intestine, and is characterised by thickening of the mucous membrane, and proliferative changes in the glandular elements, which may lead to the formation of polypoid elevations. Ulceration may follow ; and in the later stages atrophy occurs, involving, not only the mucous membrane, but also the muscular coat. The mucous membrane may exhibit pigmentation.

3. **Cœliac Disease.** Gee, in 1888, described a wasting disease of children in which there is abdominal distension without any apparent pathological lesion. This has since been described under various names by different observers, and has been more fully described by Hutchison under the term " cœliac disease." The only post-mortem finding of importance is thinning and atrophy of the intestinal wall. There is diarrhœa, the fæces are pale and offensive and always contain a considerable excess of fat. The fat is efficiently split, *i.e.*, digested, but is not absorbed by the bowel. There is also defective absorption of vitamin D and of iron, lime and phosphorus and also of Castle's extrinsic hæmopoietic factor, with the development of a hypochromic anæmia. Carbohydrates are not efficiently digested or absorbed, and may undergo fermentation. Tetany, scurvy and rickets are liable to supervene as complications.

4. **Ulceration.** This is a feature of many of the specific inflammations such as typhoid or dysentery. It may occur as small, follicular ulcers in acute and chronic catarrhal enteritis, in amyloid disease, and in some cases of chronic nephritis. So-called stercoral ulceration is frequently seen in the large intestine, and especially in the cæcum, where it may become chronic ; and, in many cases, it seems to be due to chronic irritation above a stricture of the large intestine, or to the irritation caused by an accumulation of fæces. The ulcers can be solitary and isolated, but, when numerous, the mucous membrane presents a " worm-eaten " appearance from confluence of the individual ulcers. Perforation and consequent peritonitis are possible sequelæ. Ulceration following gastro-enterostomy is sometimes found at the site of anastomosis, or in the jejunum a short distance from the opening. Whilst the hyperacidity of the stomach-contents is the main factor in producing these ulcers, it has been shown experimentally by Wilkie of Edinburgh that other factors are concerned, such as obstruction at the orifice, hæmatoma, the irritation of unabsorbed sutures, and the passage of solid food over the raw surface during the healing process. The ulcers are usually small and of peptic-ulcer type (p. 720 *et seq.*).

5. **Enteritis,** associated with superficial necrosis and fibrinous exudate, occurs in specific inflammations such as bacillary dysentery, but is also found in other conditions, *e.g.*, poisoning by corrosives, where the lesion may be in the duodenum or upper part of the jejunum—as an extension from the stomach—or, in the case of corrosive sublimate, at the lower end of the ileum and in the cæcum. Localised forms of such enteritis can be due to scybalous masses of fæces or foreign bodies. Another form is sometimes found in which

recurrent attacks occur, with the formation of mucous casts, which are passed *per rectum*. In these there is sometimes microscopical evidence suggesting a **foreign-protein susceptibility** on the part of the patient, for example, the occurrence of Charcot-Leyden crystals (Fig. 411) and large numbers of eosinophil leucocytes in the intestinal mucus. Various names are given to such forms of enteritis—"croupous," "fibrinous," "membranous," and "diphtheritic" (from the analogy of the "diphtheritic" membrane in diphtheria), etc.

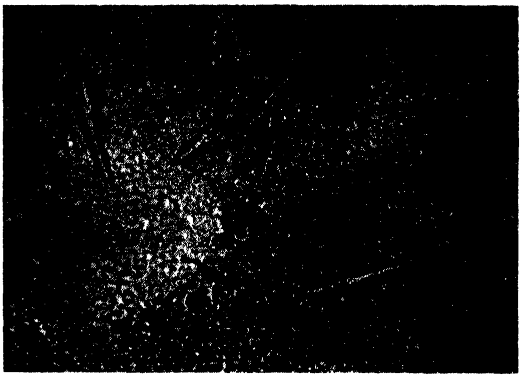

FIG. 411. "*Mucous colitis*": fresh-wet unstained film of the intestinal mucus showing Charcot-Leyden crystals, resembling those often seen in asthmatic sputum. The patient, a middle-aged woman, also had an eosinophilia of 6 to 10 per cent. in the blood. × 400.

6. **Regional Enteritis or Ileitis.**[1] Whilst this condition had been reported by various authors previously, Crohn, Ginzburg and Oppenheimer,[2] in 1932, described it in detail as a definite clinical entity, and it is therefore sometimes referred to as "Crohn's disease." Young adults of either sex, but in some series of cases males more frequently than females, are attacked, though its occurrence has been reported also in children and elderly patients.

Clinically, the condition may present as an **acute** abdominal emergency simulating appendicitis, or, more frequently, it assumes the form of a **subacute** or **chronic intestinal obstruction.** In the chronic type, there are loss of weight, attacks of diarrhœa sometimes with blood and mucus in the stools, intermittent abdominal cramp-like pains and mild fever with slight polymorph leucocytosis, and the presence of a firm palpable mass in the right lower quadrant of the abdomen. An X-ray examination after an opaque meal may show either J. L. Kantor's "string-sign" (*cf.* the analogous finding in some cases of carcinoma of the bowel—Figs. 179 and 180, p. 345) due to the great narrowing of the lumen : or complete absence of barium from the terminal coil of the ileum, but with distension of the bowel above it. If not treated appropriately, *e.g.*, by resection of the diseased portion of bowel and mesentery, or by preliminary short-circuiting followed later by resection, serious intestinal obstruction supervenes, often with the formation of fistulous openings into any neighbouring coils of intestine which have become adherent to the diseased ileum : into the bladder, vagina or elsewhere : or through the abdominal wall or in the form of para-rectal fistulæ, often with a chronic abscess or abscesses at some part of their course—fæcal material and muco-pus being discharged from these fistulæ, which are often multiple. Direct perforation into the peritoneal cavity, however, with consequent general peritonitis, is rare.

Pathologically, the terminal portion of the ileum is the usual site of the lesion, but the appendix and cæcum, and even the ascending and other parts of the colon, may be involved, and, occasionally, portions of small intestine higher up in the ileum and even in the jejunum. The affected portion of bowel is thickened and contracted, "soggy," or sometimes fairly firm in consistence, and may come to resemble a piece of irregularly-bulging, roughened hose-pipe, which, when the abdomen is opened, arrests attention, not only of the eye, but of the palpating hand. The **mucosa** is œdematous, congested and irregularly ulcerated and swollen, giving what has been graphically described as a "cobblestone-like" appearance to the inner aspect of the bowel. This is due largely to the subacute or chronic "granulomatous" reaction in the **submucous coat,** together with swelling and perhaps actual hypertrophy of the **muscular** layers. There is œdema and blotchy congestion of the **subserous** and **serous coats,** which, later, show patchy fibrous thickenings which may simulate tubercles. The **mesentery** also is œdematous, swollen and infiltrated, and the **mesenteric lymph-nodes** draining the affected area are enlarged—points to be remembered in the surgical treatment of the condition.

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[1] For reviews of the literature up to 1938–9, *see* M. Lick : *International Abstracts of Surgery*, 1938, **66**, 340 : and R. Shapiro, *American Journal of Medical Sciences*, 1939, **198**, 269. *See also* "Chronic Cicatrising Enteritis," by R. Freeland Barbour and A. B. Stokes, *Lancet*, 1936, **i**, 299, and our note on the "Reticuloses and Reticulo-Endothelioses" on p. 1262 in our Appendix at end of book.

[2] *Jour. Amer. Med. Assoc.*, 1932, **99**, 1323.

Microscopically, the usual features of a subacute or chronic inflammatory "granulomatous" process are seen, the affected walls of the bowel showing a varying admixture of polymorphs, small-round-cells, plasma-cells, larger mononuclear cells, and fibroblastic elements—with, however, no obvious "specific" features. Giant-cells are not uncommon, but there is not the typical formation of the "follicles" seen in tuberculosis. In the submucosa, the presence of certain large cells has been described, believed by most observers to be vegetable cells from the fæces trapped during the healing of the ulcers; and it is round these that "foreign-body giant-cells" have most frequently been found. Giant-cells and histiocytes may be present also in the affected lymph-nodes. The appearances resemble those seen in lymphogranuloma inguinale, but the Frei-test (p. 104) which is positive in the latter condition has been **negative** in the cases of regional ileitis tested. The ætiology is obscure. No evidence of tuberculosis or syphilis has been found and no specific causal bacteria have been isolated. From its histological resemblance to lymphogranuloma inguinale it seems not unlikely that a virus is the infecting agent (pp. 104 and 755).

7. **Uræmic Enteritis.** In chronic renal disease, associated usually with high blood-pressure and uræmia, there is not infrequently an enteritis with a varying amount of superficial necrosis and ulceration. Small hæmorrhages are frequent and often appear to be the starting-point of the lesions.

8. **Duodenal catarrh** has been mentioned above, and duodenal ulcer already described (p. 720 *et seq.*). The occurrence of duodenal ulcer as a result of superficial burns has often been described, but the relationship, if any, is doubtful, and we have not ourselves been able to confirm it from post-mortem evidence.

9. **Typhlitis and Perityphlitis** are inflammatory lesions in and around the cæcum, and have to be distinguished from appendicitis. The inflammatory reaction in the cæcum is due to the accumulation of fæcal matter, to the presence of parasites, *e.g.*, *Trichocephalus trichiuris* (*Trichuris trichiura*), or to intense catarrh arising from other causes. Ulceration is liable to be produced, and the ulcers sometimes perforate and give rise to acute inflammatory conditions with abscess-formation outside the cæcum (perityphlitis). The vermiform appendix may, in such cases, be unaffected. Acute tuberculous ulceration

in the cæcum is by no means uncommon, especially in children and young adults.

10. **Appendicitis.** Various grades of this occur, from a mild catarrhal

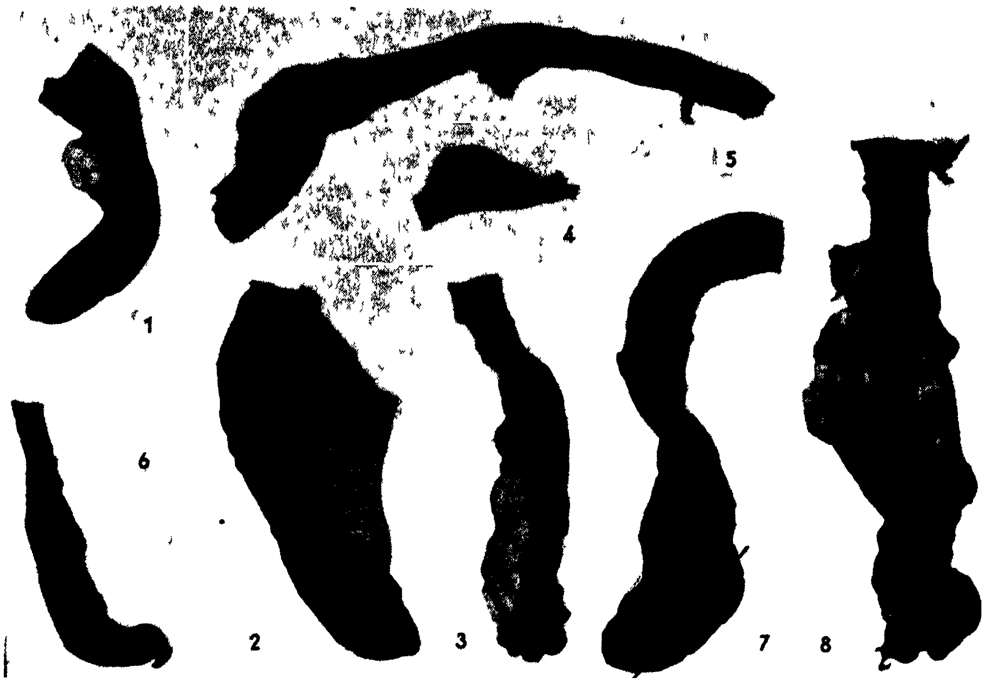


FIG 412. Appendicitis a series of appendices showing examples of various types —

1 Acute catarrhal appendicitis general congestion of mucosal and serous coats, with slight dilatation of lumen

2 Subacute, with congested swollen mucosa and slight roughening of serosa

3 Appendix removed in quiescent stage, slight congestion and swelling of mucosa only

4 Tip of appendix, completely fibrosed and solid, from old, healed appendicitis

5 Dilatation, which contained a fæcal concretion, near base (left), with thinning of wall at this area.

6. Acute gangrenous appendicitis (photograph in left corner) Tip is necrosed and proximal to it is a thick layer of fibrinous exudate around the organ

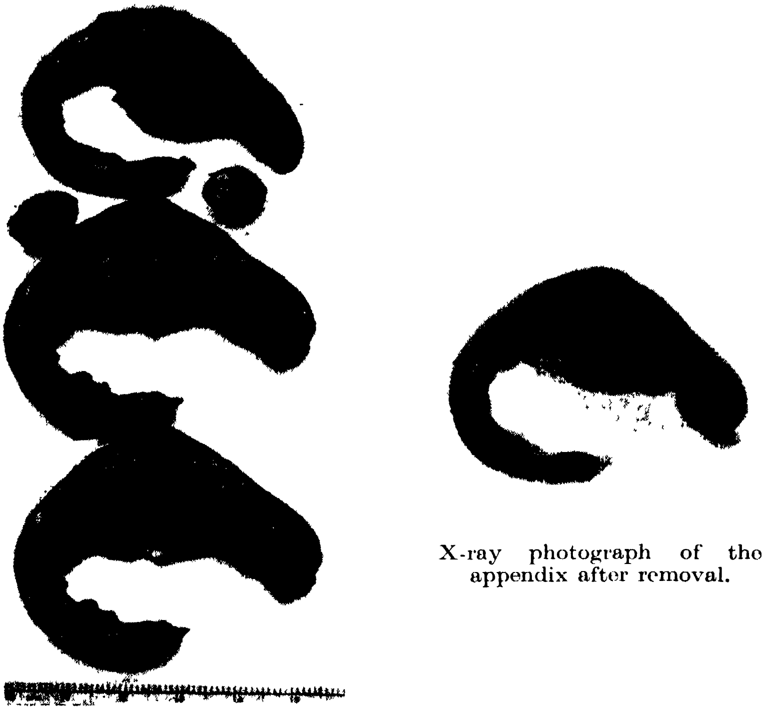
7. Acute gangrenous appendicitis with perforation near tip, fibrinous exudate proximally

8. Acute gangrenous appendicitis . appendix opened to show congestion and swelling of mucosa which is ulcerated in parts There are also bulgings, or diverticula, at intervals along the organ.

inflammation of the mucosa to a severe gangrenous lesion of all the coats of the appendix (Fig. 412).

In the **catarrhal form,** there is congestion and œdema of the mucosa with excess of mucus and slight shedding of the superficial cells, or even slight mucosal erosions. The lymphoid tissue is swollen, with some hyperplasia of its nodes. There is slight to moderate acute inflammatory cell-infiltration of the mucosa. The muscle is congested, the peritoneal coat often unaffected. The condition may clear up and leave no trace. Frequently, however, it recurs, the recurrence being determined by whatever causal factors were responsible for the first attack, or due to effects left by the first attack. Thus the catarrhal debris sometimes forms the starting-point of fæcal concretions (Fig. 413) or the mucosal changes—swelling, mucus, etc.—can lead to obstruction of the lumen from the accumulation of infected debris. Such an appendix is liable to become dilated and perhaps gangrenous, and will rupture readily in a succeeding attack.

Acute suppurative (gangrenous) appendicitis may, as indicated, follow a mild attack or occur *de novo.* The lesion is often focal, at the tip or in the body of the appendix. At times it extends around the lumen in a fashion suggesting acute vascular obstruction of a segment of the organ. The affected area, if gangrenous, is necrotic, black or greenish. It frequently perforates acutely, or a portion of the organ, *e.g.*, the tip, sloughs, and general peritonitis results. Where perforation is not so abrupt, there will be local fibrinous exudate on the serous coat of the appendix, with intense congestion of all its coats and, microscopically, all the signs of an acute inflammation—infiltration with leucocytes, etc., together with a polymorphonuclear leucocytosis in the blood. The inflammatory reaction also spreads to the mesentery of the organ, extending along the lines of the vessels, some of which may become thrombosed.



X-ray photograph of the appendix after removal.

FIG. 413. *Very chronic appendicitis* in a female aged twenty years, who had had *no* ascertainable previous clinical symptoms to suggest its presence, until a sudden acute exacerbation on the morning of the day on which the appendix was removed. Two large firm *calcified fæcal concretions* (of the type that used to be mistaken for "cherry-stones") are seen embedded in the lumen about its centre. These were surrounded by blood-stained mucus: and, in the lumen between them and the bulbous tip of the organ (to the right), was a series of small pale-yellow-ochre-coloured soft and friable more recent concretions, composed mostly of aggregations of fatty-acid crystals. (By courtesy of Miss Alfreda H. Baker, Dr. Bowden and Miss B. Carnegie Dickson, Oster House Emergency Hospital, St. Albans.) × 7/10ths natural size.

There are milder grades of acute appendicitis, without perforation, which heal, with the production of adhesions to surrounding structures from organisation of the local peritonitis. Portions of the damaged organ may heal, with fibrous obliteration of the lumen. If this occurs in the tip or distal end, there remains an attenuated fibrous cord ; but if in the middle or at the base, the fibrosed scar leads to obstruction and consequent distal dilatation—as described for the catarrhal form. Such obstruction is the usual cause of **mucocele** of the appendix from continued secretion by the mucosal cells into the occluded portion or the entire length of the organ. A mucocele can attain a large size, even coming to resemble a portion of intestine. It may rupture and it is an ever-present source of danger from infection of its stagnant contents. **Diverticula** sometimes develop along the lines of the vessels entering from the mesentery of the appendix.

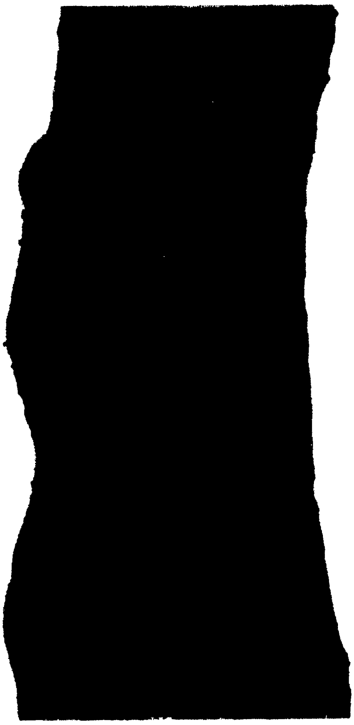


Fig. 414. Ulcerative colitis, showing large ulcerated areas alternating with ragged tags of surviving, swollen mucosa.

Complications and Sequelæ. Some of these have been mentioned above—perforation, peritonitis, adhesions, obstruction, concretions. The peritonitis, if local, can result in a **peri-appendicular abscess** the position of which—retro-cæcal, pelvic, etc. —depends on the position of the appendix itself ; or the infection of the peritoneal cavity may be general, perhaps with focal accumulations, *e.g.*, subphrenic abscess. A rare and very fatal sequel is **pylephlebitis,** and **portal pyæmia**, where septic thrombosis in the appendicular veins extends up into the portal vein, with the production of multiple abscesses in the liver. Recurrent attacks, any one of which is liable to end with the above sequelæ, are frequent, and **chronic appendicitis** is in reality a succession of acute exacerbations in an already damaged appendix. Such an organ when finally removed is often greatly thickened and scarred. In the quiescent or " healed " stage there is much lymphoid infiltration of all coats ; and frequently also eosinophil leucocytes are present in abundance, especially in mucosa and submucosa. In the more acute phases, polymorph leucocytes are numerous.

Ætiology. The initial cause is often obscure. Appendicitis may occur at any age. In some cases the anatomical characters, or the position of the appendix, favour the occurrence of lesions—thus various kinks and twists of the mesentery, or pressure from a distended cæcum, lead to mechanical obstruction, with, or without, interference with its vascular supply, so favouring the activities of local bacteria, or bacteria that happen to be in the blood-stream. Extension of infection from the cæcum is possible, but rarely demonstrable. No specific organisms have been found, though in some acute cases pure cultures of streptococci have been obtained. Parasites such as thread-worms (*Enterobius* or *Oxyuris vermicularis*) and whip-worms (*Trichurus* or *Trichocephalus*) have been blamed, but they are frequently present in the organ without any obvious appendicitis. Fruit-seeds and other foreign bodies have likewise been suspect, but with insufficient evidence; and moreover, small fæcal concretions have been mistaken for these (Fig. 413). In most cases the specific cause is not identified. Once the appendix is damaged, its liability to subsequent attacks is easily understood and explicable, as indicated above.

11. **Colitis.** Under this term various authors describe inflammatory infections of the colon which show all degrees of implication of the intestinal mucous membrane, from a mere slight surface catarrh, sometimes with excess of mucus, up to severe and extensive ulceration.

Mucous colitis is a common condition in which there is variable catarrhal inflammation of the mucosa with passage of excessive mucus. Its ætiology is obscure, but, as noted above (p. 743), some cases appear to be related to foreign-protein susceptibility; frequently there is an associated "neurasthenia."

Ulcerative Colitis (Fig. 414). The condition is characterised by diarrhœa, and the stools contain blood, pus, mucus, and sometimes sloughs of the mucous membrane. Various bacteria are associated with such intestinal affections, but no one special causal organism has been detected. In some instances, the streptococcus seems to be the most likely infecting agent; in others, some member of the paratyphoid or dysentery group is the predominating organism. Certain cases, commencing in the cæcum or hepatic flexure and extending down the bowel to the pelvic colon, have been described as "**regional colitis**" (*cf.* "regional ileitis," p. 743).

12. **Specific Inflammations of the Intestines.**[1] These, though in many respects similar to the forms above described, have certain distinctive characteristics, and are caused by specific bacteria or by parasites.

(*a*) **Dysentery.** This term has been, in recent years, applied more or less indiscriminately to any condition producing blood and mucus in the stools, or even to diarrhœa alone, but we here confine it to the two distinct forms, that due to *Entamœba histolytica* and that caused by the bacilli of the dysentery group (Flexner, Shiga, etc.). While amœbic dysentery is mainly a tropical or subtropical condition, sporadic cases have been reported in persons who have never been out of the British Isles, infected possibly by "carriers" from abroad. Bacillary dysentery is also common in warm countries, but is by no means confined to them.

Amœbic Dysentery. The presence of *Entamœba histolytica* (pp. 363 and 778) in connection with this disease is so striking that no doubt can now be entertained as to its causal relationship, but, as Dobell says, it is a "pathogenic parasite in a restricted sense. It is always a destroyer of tissue, but by no means always productive of disease. The usual type of human infection is that exemplified by the carrier of the parasite." And again: "Every healthy carrier has the lining of his large bowel more or less ulcerated; though the ulceration may be, and probably often is, superficial and almost invisible *post mortem* to the naked eye. But even extensive ulceration may exist without any dysenteric symptoms being evident."

The disease is usually contracted by the ingestion of infected food. Carriers are reservoirs of infection, as they pass the encysted forms in their fæces. Flies feeding on such fæces ingest the cysts, which are resistant, and, later, these infected flies alighting on foodstuffs, regurgitate their stomach-content, including the cysts, and thus contaminate the food. Obviously, prevention of infection is possible by adequate sanitary measures.

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[1] For fuller accounts of many of these conditions see "The Dysenteric Disorders," by P. Manson-Bahr, 1939, and "Bowel Diseases in the Tropics," by Leonard Rogers, Oxford Medical Publication, 1921.

The **amœboid** form of the parasite dies and disintegrates soon after leaving the body in the fæces, and does not take part in propagating the disease; and, therefore, in order to detect the amœboid form in the fæces or tissues, these must be examined immediately after removal from the body. When living-conditions become unfavourable for the amœba, as for example during the process of healing, **cysts,** usually containing **four** nuclei, are formed. These small resistant encysted forms when ingested pass unharmed through the stomach of the human host into the intestine, lose their enveloping cyst-wall and become actively amœboid in the lower bowel. They then make their way into the mucosa and submucous coat, upon which they feed, and in which they have their habitat. Here, in the carrier, they set up only a minor degree of irritation. In cases, however, in which they produce active disease, they cause considerable irritation and local destruction of the tissues. They penetrate into the lymph-spaces and into the veins, and it is by way of the radicles of the portal vein that they reach the liver. The lesions which occur in any part of the large intestine show a great variety of appearances depending on the stage and intensity of the

Fig. 415. Amœbic dysentery. Colon, with numerous irregular ulcers of all sizes, with undermining of edges. Intervening mucosa shows little change.

Fig. 416. Acute bacillary dysentery. Colon, showing widespread superficial necrosis of the swollen, congested mucosa.

infection, and are found especially in the cæcum and ascending colon. The earliest lesions are in the form of small nodules, from the size of a pin's head to that of a pea, projecting above the general level and showing a central, yellowish area of necrosis, covered with intact mucous membrane, or with the mucosa ulcerated at the summit of the nodules. As a result of this necrosis, rounded or oval ulcers, with raised undermined edges, and containing lemon-yellow gelatinous debris, are produced (Fig. 415).

As the disease progresses, the mucous membrane becomes greatly thickened and œdematous. Ulcers may then show all transitions, from slight erosions to extensive and deep excavations with irregular outlines. There may be fibrinous exudation and hæmorrhage on or into the mucous membrane. Occasionally the necrotic changes are so intense as to involve extensively the muscle-coat, and bring about perforation into the peritoneal cavity or extra-peritoneal tissues. Healing can occur either if the ulcers are still small—in which case little or no trace of them is left: or later, in which case, owing to the more extensive ulceration, considerable scar-tissue is likely to form.

The lymph-nodes draining the ulcerated areas may show some enlargement, but this is not a pronounced feature. In the **liver,** the most important secondary lesion is the presence of one or more **amœbic abscesses** (p. 778); but cloudy swelling and fatty degeneration of the liver-cells are common ; and, frequently, there is infiltration of the portal spaces with lymphocytes and plasma-cells.

Entamœba histolytica (p. 363), as already noted, may be present in large numbers in the fæces: in the submucous coat at the periphery of the ulcers : as well as in the submucous tissue, in the lymphatic spaces, and in the veins at some distance from the ulcerated area. The parasites may also be found in the dilated subserous veins and even in the portal veins.

Bacillary Dysentery (Fig. 416, p. 749). This form of the disease is caused by certain bacilli of the dysentery group of which the type described by Shiga is perhaps the most important. (For types and their characters, see text-books on Bacteriology.)

The pathological condition is essentially a diffuse toxic lesion with intense inflammatory reaction, necrosis and ulceration. The large intestine, especially its descending portion, mainly is affected, but the lowest part of the ileum may also be involved. Both bacillary and amœbic forms of dysentery may be present in the same patient.

In rapidly fatal cases of uncomplicated bacillary dysentery, the mucous membrane of the intestine is swollen, intensely congested and hæmorrhagic, and the rugæ are prominent, and covered with viscid, blood-stained mucus. In cases surviving till somewhat later, the mucosa is necrotic, greyish and with a pseudo-membranous exudate of so-called "diphtheritic" type, often associated with deep necrosis in the form of dirty-brown or blackish blood-stained sloughs—the gangrenous type. The submucosa shows infiltration with inflammatory cells and serous exudate. At a still later stage, large ulcers are found, with undermined edges, and extending down to the muscular layer. In extreme cases, the whole of the glandular tissue in the affected area may be destroyed, the mucous coat disappearing completely, and the submucous coat showing extensive sloughing and infiltration by inflammatory cells, fibrin, and blood. These cells, largely of polymorph type, with mononuclear cells in the later stages, are present throughout the coats, as well as collected in special foci round the blood-vessels. Elsewhere than in the bowel itself—except perhaps for the occasional occurrence of secondary suppurative infection of the gall-bladder or bile-ducts, there are no characteristic lesions in cases of bacillary dysentery, but changes similar to those found in any infective or toxic disease may be present in various organs and tissues—and arthritis has been described as occurring in the larger joints.

Results. In some cases, if the attack has been slight and the ulceration only superficial, and particularly if treated **early** with sulphaguanidine [1] (sulphanilylguanidine), with or without the specific serum, there may be complete restoration of the mucous membrane. In other instances, the healing may be so complete, that the evidence of former ulceration is rendered apparent only by the presence of thin translucent areas in the wall of the bowel. Usually, however, especially in untreated or inadequately-treated cases, when healing takes place, cicatrices are left, which are generally darkly pigmented and may give rise to contraction and to stricture of the colon. As a result of the stricture, dilatation of the intestine above the diseased portion may take place, and a secondary follicular ulceration, which is quite independent of the dysenteric infection, may follow. The condition may become chronic, and the original infection may be replaced by non-specific organisms—streptococci, etc. The blood shows a polymorph leucocytosis during the active stage of the disease.

Asylum- (or **Institutional**) **Dysentery.** There is general agreement that the causal organism of this form of ulcerative colitis is one of the colon-typhoid group of bacilli. From some cases *Bacterium dysenteriæ* has been isolated and in most of these it has been of the Flexner type.

A certain proportion of cases of so-called sporadic dysentery may be due to *Bacterium dysenteriæ*, but many are undoubtedly caused by other organisms, *e.g.*, *Bacterium paratyphosum* (*Bacillus paratyphosus* or *Salmonella schottmülleri*), Morgan's bacillus (*Salmonella morgani*), etc. Thus the dysenteric symptoms, which are not uncommon in children in summer-diarrhœa, may be due to Morgan's bacillus or to other members of the colon-typhoid group, and probably also, in some cases, to bacteria of other groups ; such cases are, therefore, not in any way related to true dysentery.

(*b*) **Cholera.** In this disease, of which the causal agent is the cholera vibrio (*Vibrio choleræ* or *V. comma*) or the comma-bacillus of Koch, the mucous membrane of the intestine becomes swollen and markedly congested, especially in the region above the ileo-cæcal valve. The superficial mucosa undergoes necrosis and in the exposed surface, in the crypts of Lieberkühn and between the lining-cells, the vibrios are found. The lymphoid follicles may also show swelling and congestion. Small hæmorrhages may be present, and the outer surface of the intestine has a rosy red injected appearance. The lumen of the bowel contains a quantity of watery fluid in which float ragged whitish flakes consisting of mucus, epithelial debris and bacteria—these constituting the characteristic "rice-water stools," in which the organisms may be found in practically "pure culture." The circulating blood is sometimes viscid in consistence on account of the constant diarrhœa and the consequent great " drying-up " of all the tissues.

(*c*) **Typhoid Fever.** The *Bacterium typhosum* (*Bacillus typhosus* or *Eberthella typhi*), which is causal of this disease, is present in the intestinal contents, the lymphoid follicles of the intestine and lymph-nodes, and in the liver, kidney, and spleen—being generally seen, in sections of these tissues, in small clumps

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[1] E. K. Marshall, *et al.*, *Bull. Johns Hopkins Hosp.*, 1940, **67**, 163; 1941, **68**, 94 ; and *Lancet*, 1941, **i**, 388.

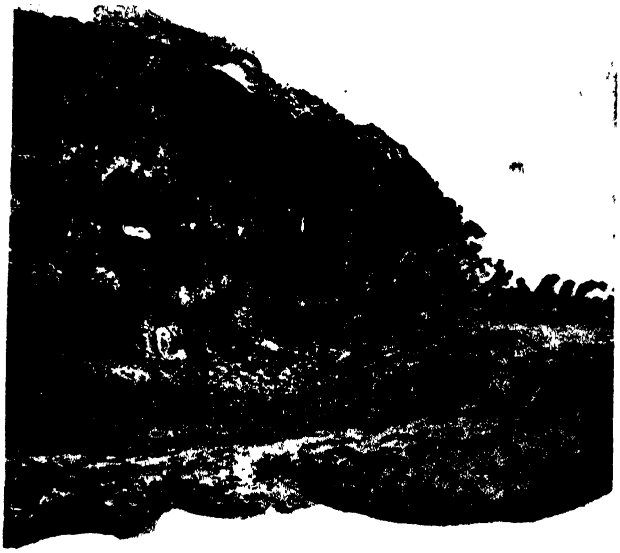

FIG. 417. Intestine from an early case of typhoid fever, showing great swelling of a Peyer's patch or aggregated lymphoid nodule. × 15.

or masses. It can usually be detected by blood-culture in the earlier stages of the disease and for a longer period in the bone-marrow, from which it may be obtained by "medullo-culture" (p. 606); it may be found in the urine and gall-bladder. In the urine and gall-bladder, the organism may persist for a very long time, the infected individual thus becoming a "carrier" of the disease—the bacilli are sometimes discharged perhaps intermittently for several, and in some cases for many, years in the urine and in the fæces. Examination of the blood in the early stage of the disease is important in diagnosis, as the organism may be demonstrated in cultures from the blood or bone-marrow before the agglutinins have developed in sufficient quantity to give an agglutination-reaction.

Pathological Anatomy. The main seats of the lesion are the lymphoid structures of the lower part of the small intestine—the aggregated and the solitary follicles—the mesenteric nodes and the spleen. During the first week of the disease, the solitary lymphoid nodules and the Peyer's patches

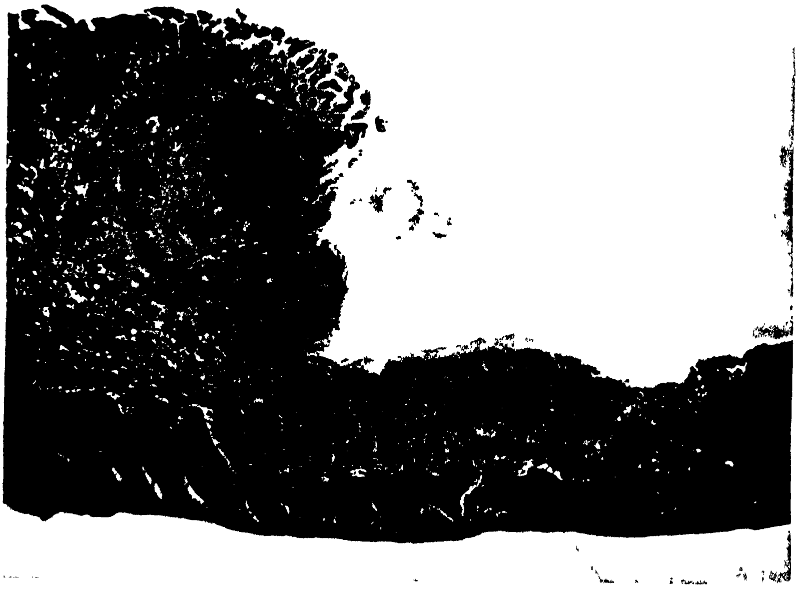

FIG. 418. Intestine from a case of typhoid fever, duration about three weeks, showing swelling and ulceration of a Peyer's patch or aggregated lymphoid nodule. × 16.

become swollen and inflamed, raised above the surface of the intestinal mucous membrane, and pale or somewhat reddish in colour. The solitary lymphoid nodules in the large intestine may also be swollen. The

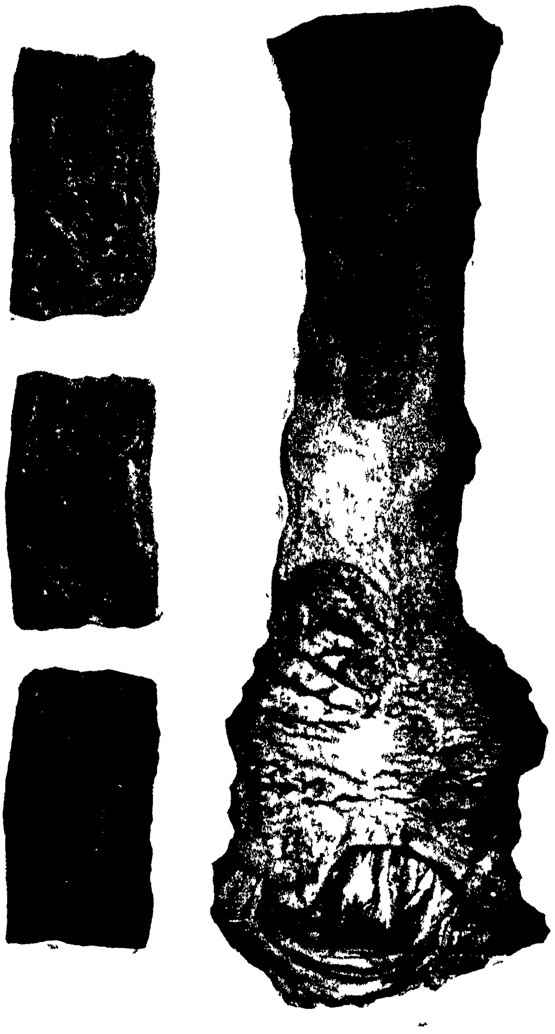

FIG. 419. Portions of the intestine from cases of typhoid fever of about three weeks' duration.

(*a*) Lower end of ileum and ileo-cæcal junction, showing great swelling of the aggregated lymphoid nodules and solitary nodules, preceding ulceration.

(*b*) Pieces of small intestine showing the early stages in the formation of ulcers. The upper piece shows a small slough in a swollen aggregated nodule. The middle portion shows the separation of two sloughs in a similar patch. The lowest piece shows a small ulcer forming in a swollen solitary nodule. [1]

initial swelling in some of the nodules may subside ; whilst in others it increases in amount and the nodule becomes firmer and paler (Fig. 419). Small areas of necrosis appear in the swollen part, and these, increasing in size, coalesce with one another and so form irregular sloughs, which are usually bile-stained. Towards the end of the third week the sloughs become separated and irregular ulcers are formed (Figs. 417 to 419). The ulcers are usually oval, their long axis being parallel with that of the intestine. The floor may be irregular, if the sloughs have not completely separated, but it may be smooth and be formed by the muscular wall. The edges of the ulcers are undermined. If the ulcerative process does not penetrate deeper, the peritoneal coat shows very slight alteration. The necrotic changes may, however, spread through the muscular and peritoneal coats, and a perforation—usually of small size—with escape of fæcal contents into the peritoneal sac and resulting general peritonitis, may occur, or erosion of blood-vessels may lead to severe and even fatal hæmorrhage. On microscopical examination, the swelling of the aggregated and solitary nodules is seen to be due largely to a proliferation of the reticulo-endothelial cells. These cells are actively phagocytic, and some of them may fuse, to form giant-cells which retain their phagocytic properties. When recovery takes place, the ulcer cicatrises and the epithelium grows over the surface from the edges. The cicatrix is often pigmented and may remain permanently as a flat area in which the intestinal wall is thin and translucent. The destroyed lymphoid tissue may not be restored. If the ulcer has been small and superficial, healing may occur and leave no visible trace.

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[1] Drawings from these preparations appeared in Lancereaux's "Atlas of Pathological Anatomy" (English Translation by the late Professor W. S. Greenfield), Plate LXIX.

The mesenteric lymph-nodes corresponding to the infected area become swollen and softened, and small areas of necrosis (focal necrosis) are seen in them. The spleen is enlarged, usually somewhat firm, and of a dark red colour, and, on microscopical examination, is found to contain small clumps of the bacilli. The liver, and more rarely the kidneys, may show areas of focal necrosis, whilst cloudy swelling and fatty changes are almost constant features.

In an uncomplicated case of typhoid, the blood shows a **leucopenia,** a finding which is useful in differential diagnosis. Acute nephritis, bronchitis, bronchopneumonia, ulceration in the larynx, myocarditis, Zenker's degeneration of muscle, necrosis and abscess-formation in bones, usually subperiosteal—especially in the ribs and the tibiæ—arthritis, phlebitis, or meningitis, may occur as complications.

(*d*) **Paratyphoid Fever.** This disease is due to *Bacterium paratyphosum A* (*Salmonella paratyphi*) or *Bact. paratyphosum B* (*Salmonella schottmülleri*), and may give a picture clinically and pathologically indistinguishable from that of typhoid. Certain strains associated with meat-poisoning, may produce a more diffuse enteritis. Diagnosis depends on bacteriological examination, the identification of the infecting organism, and the agglutination of known strains of it by the patient's serum.

In the cases resembling typhoid, the lesions are so similar that any description would be but repetition of that given for typhoid. The same dangers of hæmorrhage and perforation are present. Paratyphoid " carriers " also occur.

Like *Bact. typhosum,* each type of the organism occurs in the fæces and in the urine, and may be isolated from the blood in the early stages of the disease. Later, in some cases in which blood-cultures have been, or have become negative, the organism has been successfully grown from biopsy-specimens of the bone-marrow obtained by sternal puncture (p. 606). *Bact. paratyphosum A* can be distinguished from *Bact. paratyphosum B* and other members of the group by its agglutination-reactions.

(*e*) **Tuberculosis of the intestines** (Fig. 39, p. 71 and Fig. 420, below) is associated especially with pulmonary tuberculosis, but it may occur as a primary affection of the intestine, especially in young children. The cause of infection is the swallowing of tuberculous sputum, or the ingestion of milk or other food containing tubercle bacilli. In the young adult, the ileo-cæcal region is occasionally the site of extensive tuberculous infiltration, causing thickening of the wall of the bowel and leading to obstruction, but recent investigation, especially in America (at the Mayo Clinic and the Mount Sinai Hospital, New York) points to the probability that many of the cases diagnosed in the past as "tuberculous" have been examples of **non-specific granulomatous regional ileitis** (**"Crohn's disease,"** p. 743). In rare instances, **acute** tuberculous ulceration leads to perforation, but the patient is usually protected against this complication by the occurrence of thickening of the peritoneal coat and perhaps by the formation of adhesions (p. 71). Many cases of **fistula-in-ano,** previously regarded as tuberculous, are now believed to have been complications of regional ileitis or of ulcerative colitis. Where the diagnosis of tuberculous fistula has been confirmed histologically or bacteriologically, it has almost always been secondary to pulmonary tuberculosis (p. 72).

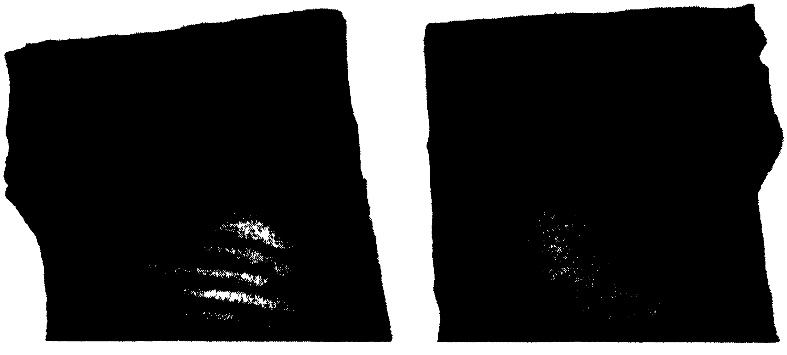
(*a*) (*b*)

FIG. 420. Tuberculous ulceration of intestine.

(*a*) Mucosal surface, showing the ulcer extending transversely around bowel, base ragged, edges irregular and thickened.

(*b*) Serous surface external to the ulcer, over which can be seen tubercles and delicate tags of fibrous adhesions.

(*f*) **Syphilis** (p. 88) rarely produces any definite localised lesions of the intestine, but gummata occasionally occur, with ulceration, cicatrisation, and stricture. Primary sores about the anus are found, especially in women ; but, in the past, lymphogranulomatous lesions (*see* below) have sometimes been mistaken for those produced by syphilis.

(*g*) **Actinomycosis** (p. 91). In the bowel, the cæcum and appendix are the commonest sites of actinomycosis, but the pelvic colon may be attacked. Abscesses and sinuses are formed and the abdominal parietes become infiltrated.

(*h*) **Lymphogranuloma inguinale** (pp. 88, 104 and 744). In this condition, the pelvic colon and the rectum may be converted into a rigid tube. The peritoneum is thickened, and, under this, is a uniform layer of dense fibro-adipose tissue, sometimes half-an-inch in thickness. The muscular layer may be atrophied, or may show little change ; but the submucous layer is greatly thickened by an overgrowth of dense fibrous tissue. By contraction of this tissue, the mucous membrane is thrown into folds with deep recesses between them, and ulceration takes place in these recesses. No evidence of malignant disease is found, but the tissues are infiltrated with chronic inflammatory cells. This rectal condition is now regarded as the result of a virus-infection (p. 104). It is found especially in women, first as a small, localised, venereal infection about the vagina. Owing to the distribution of the lymphatics in the female, the spread is to the wall of the rectum, producing inflammatory infiltration with ulceration, and later fibrosis and contraction. In the male, the initial venereal infection is on the penis and spread is to the inguinal lymph-nodes—hence the name.

TUMOURS OF THE INTESTINE :—

Tumours are common in the large intestine but rare in other parts of the bowel. Of **simple tumours**, fibromas, myomas, lipomas, myxomas and papillomas are occasionally found, usually in the form of polypoid growths projecting into the lumen. Of these, the **papilloma**—of columnar-cell type—is perhaps the commonest, occurring in the colon. These papillomas may be multiple, as seen in the rare condition of **polyposis** of the colon. The interest of this disease is that it occurs in families, as noted by Dukes (1930) : and that the papillomas—which may be pedunculated or sessile—tend to become malignant. Children and young adults may be affected. Occasionally a papilloma, or other similar growth, may be the starting-point of an intussusception.

Of **malignant tumours,** carcinoma is much commoner than sarcoma. **Lymphosarcoma** may occur and form large masses in the intestinal wall. Masses similar to these and composed of lymphoid cells may be found throughout the mucosa of the intestine in some cases of lymphatic leukæmia. Ulceration of, or hæmorrhage from, such nodules may occur. **Carcinoma,** usually of adenomatous, less frequently of spheroidal-cell type, is found in the **duodenum** in the neighbourhood of the ampulla. It is rare in the small intestine, but common in the **colon**, especially at the flexures and in the rectum. It forms a large fungating mass which tends to ulcerate and bleed, or it occurs as a firm, annular growth around the lumen—" ring carcinoma "—causing progressive obstruction (Figs. 179–180, p. 345). **Mucinoid degeneration** is frequently present in varying degree (" colloid carcinoma," p. 349). In the **anal canal** the commonest type of carcinoma is the **squamous epithelioma**.

The growth may remain localised for a considerable time—a feature favourable for surgical removal—or it may extend through the coats of the gut to the peritoneum, and also to the adjacent lymph-nodes. Metastasis to the liver is of frequent occurrence. Perforation of a carcinoma is uncommon.

Secondary deposits in the intestine from primary sites elsewhere may occur, usually from neighbouring structures such as the ovary, uterus or kidney.

Carcinoid tumours (also known as argentaffine, or chromaphil, tumours, from their staining affinities) are found in the **small intestine,** especially the ileum, and in the **appendix**. They are usually benign, though malignant forms have been found, with metastases in lymph-nodes and liver. They consist of solid masses of rather small, uniform, darkly-staining cells which Masson considers arise from cells of primitive nerve-cell type, but which other writers regard as secretory in character. These tumours may cause obstruction in the intestine or appendix and are a rare cause of appendicitis. (For the connection of these argentaffine cells of the gastro-intestinal tract with the production of Castle's "intrinsic factor," hæmopoietin, *see* pp. 647–9.)

OBSTRUCTIVE EFFECTS IN INTESTINES :—

The Effects of Obstructive Lesions of the Intestine. In the foregoing descriptions of various lesions in the intestines, a frequently-mentioned result has been **obstruction,** with its attendant changes. Such obstruction may be **acute** or **chronic,** and the former may occur alone or supervene on the latter. Obstruction is, clinically, an important and serious condition, usually requiring active surgical interference, and for this reason is dealt with in detail in surgical text-books.

Causes. These may be **mechanical**, often with accompanying **vascular** interference, *e.g.*, congenital atresia : bands of adhesions : strangulation in hernial sacs : volvulus : intussusception : pressure from without, *e.g.*, by tumours : impaction of foreign bodies such as dentures, plum-stones, or, occasionally, of a large gall-stone : infarction, especially of the superior mesenteric artery : reduction of lumen by tumour, or by cicatrising ulceration as in tuberculosis and chronic dysentery. Interference with **nervous mechanism** is seen in the so-called " paralytic ileus ", which is one of the serious complications of peritonitis and after abdominal operations. In this condition (*see* footnote, p. 734), the inhibitory sympathetic nervous mechanism seems to be stimulated so that no peristalsis occurs and the intestines become inert and distended with gas and fluid. In the rare form of " spastic ileus " (which is the literal connotation of the word " ileus ") there is firm contraction of segments of the intestine, usually the colon.

General Effects. In **acute** obstruction—other than the nervous forms—the intestine proximal to the obstruction becomes distended and filled with fluid content. There is frequently necrosis and gangrene, from vascular occlusion and bacterial activity. In the **chronic** form, which is most commonly seen in the slowly progressing " ring-carcinoma " of the colon, there is accumulation of bowel-content, with hypertrophy of the muscle-wall proximal to the obstruction and often vigorous peristalsis. The distal part of the intestine is collapsed and may be atrophied. Such chronic obstruction may become " acute," *i.e.*, complete, from sudden occlusion of the already narrowed opening, *e.g.*, by a fæcal mass or foreign body or by superadded congestion or œdema. (*See* Figs. 179–180, p. 345.)

Obstruction of the small intestine, especially if high up, is more dangerous than of the large intestine. In acute obstruction of the small intestine, there is profound prostration and often severe vomiting. The patient is in a "toxic" state and may succumb rapidly. The cause of this toxæmia has been much discussed and, though stress is laid on one or other factor by different authorities, probably several factors are responsible, in varying degree in different cases, and in the same case at different periods. The two main factors, in addition to the non-absorption of food-elements, especially proteins, and of fluid, are : (1) **Loss of chlorides,** and (2) **bacterial infection.** The first—loss of chlorides—is due to the severe vomiting, and to the accumulation of fluid and chloride in the obstructed area. Incidentally, such deprival of fluid leads to a dehydration of the patient's tissues. The second—bacterial intoxication—is undoubtedly a factor, as shown by B. W. Williams (1926–1927), who demonstrated the toxin of *B. welchii* (*Clostridium welchii*) in the contents of obstructed loops, both in man and in experimental animals. Whether such toxin is to any extent absorbed from the obstructed loop is uncertain, though treatment with the specific anti-serum is associated with clinical improvement.

PARASITES :—

Protozoal Infections. Various protozoal parasites are found in the alimentary tract. Except in the instance of *Entamœba histolytica*, the *rôle*, if any, which some of these play in the production of irritation or actual disease of the bowel is not yet fully established. Diarrhœa may be present in cases in which these parasites are found, yet the same parasites are not infrequently found in the faeces of apparently normal individuals. Of these parasites the most important are :—

Entamœba histolytica, p. 363
Entamœba coli, p. 366, and *Endolimax nana*, p. 367.
Trichomonas hominis, p. 371 (large intestine and colon).
Giardia (*Lamblia*) *intestinalis*, p. 371 (upper part of small intestine).

Occasionally *Tetramitus mesnili*, *Cercomonas* and other unimportant protozoal parasites are found.

Bilharziasis or Schistosomiasis. The ova of *Schistosoma mansoni*, the specific parasite of Intestinal Bilharziasis or Schistosomiasis (p. 386 *et seq.*), may cause very considerable irritation of the rectum, with the production of numerous large papillomatous growths in the region of the anus and extending well into the rectum. The thickening may resemble carcinoma, and, in some cases, apparently, carcinoma supervenes as a secondary result of the irritation. *Schistosoma hæmatobium* (*Bilharzia hæmatobia*, p. 386), either alone, or in association with *S. mansoni* (p. 391), is also found occasionally in the rectum.

Among other animal parasites occurring in the intestine may be mentioned *Tænia saginata* and *Tænia solium*, *Diphyllobothrium latum*, *Ascaris lumbricoides*, *Ankylostoma duodenale*, *Enterobius vermicularis*, *Trichurus trichiura*, *Paragonimus westermanii*, *Heterophyes heterophyes*, etc. These are described under Animal Parasites (p. 393 *et seq.*). They may give rise to enteritis with a varying degree of diarrhœa, and mucus and blood may be found in the stools, or there may be no local symptoms.

DISEASES OF THE PERITONEUM

Congenital Abnormalities. There may be an exaggeration of certain of the normal pouches, abnormal shortness of the mesentery, laxness of the various ligaments, or the persistence of processes and connections which in the ordinary course of development become obliterated. The occurrence of dermoid cysts, and other cystic developments of unknown origin (air-cysts, etc.), has been recorded.

Circulatory Disturbances :—

(*a*) **Acute Congestion** (*see under* Inflammation, p. 17).

(*b*) **Chronic venous congestion,** resulting from any of the usual causes (p. 148 *et seq.*—*see* p. 152), may show itself in the peritoneal sac. The peritoneum becomes œdematous, and accumulation of fluid occurs. The fluid may be clear, or blood-stained from rupture of the distended vessels.

(*c*) **Hæmorrhages,** in the form of petechiæ, are found in various septic and hæmorrhagic diseases, and in parts adjacent to acute inflammatory foci. Minute hæmorrhages occur in chronic venous congestion, and in phosphorus-poisoning, snake-bite, etc. When recent, the petechial hæmorrhages are bright-red in colour. At a later period, the remains of these are frequently seen as small, black, pigmented spots immediately under the serous surface. Larger and sometimes massive hæmorrhages may be due to traumatic injuries to the abdomen, such as violent blows, the blast of explosives, or crushing or penetrating wounds, by which laceration or rupture of one or more of the abdominal viscera may be produced.

If an organ has been previously diseased, it is more prone to such damage. Thus an enlarged malarial spleen (pp. 382, 690 and 695) may rupture from slight injury—it may, however, even rupture " spontaneously." Rupture of an extra-uterine pregnancy is a not infrequent source of hæmorrhage. Less commonly, rupture of cysts, *e.g.*, of the ovary, infarction of the intestine, and, in some cases, cancer or tuberculosis of the peritoneum may occasion hæmorrhage.

The blood-effusion may spread for a variable distance throughout the retroperitoneal tissue or between layers of peritoneum, as in the mesentery, as well as being free in the abdominal cavity.

(*d*) **Ascites**[1] develops as part of general dropsy in cardiac or in renal disease ; or it may be due to obstruction of the portal circulation, especially in cirrhosis or cancer of the liver. Chronic peritonitis may lead to accumulation of fluid in the sac, but does not necessarily do so. The fluid is usually clear and colourless, or perhaps yellowish in colour, but it is sometimes hæmorrhagic in character. Where there has been obstruction or rupture of lymphatic channels, for example in some filarial diseases or in tuberculosis, the fluid appears milky from the presence of finely-divided fat or chyle—**chylous ascites** (p. 425). A fluid, somewhat resembling in its naked-eye characters that of chylous ascites, is occasionally seen in cases of cancer—where there is considerable degeneration of the cells, the admixture of the cells containing fatty particles with the fluid giving it a milky appearance—in tuberculosis of the mesenteric lymph-nodes, and also in some obscure conditions in which the particles are not fatty but albuminoid.

As a result of the ascites, chronic fibrous thickening of the peritoneum is not infrequent.

INFLAMMATION, or PERITONITIS :—

Peritonitis occurs as a result of the direct spread of infection through a damaged, but not necessarily perforated, gastric or intestinal wall ; or it may be secondary to appendicitis : to the escape of the contents of the stomach or of the intestine into the peritoneal sac : or to the secondary spread to the peritoneum of an inflammation—suppurative or non-suppurative—in or round the intestines or other abdominal or pelvic organs, *e.g.*, the uterine (Fallopian) tubes. Direct spread through the diaphragm from the pleural cavity or extension from septic wounds in the abdominal wall may occur. A direct infection of the peritoneum is not common, but may arise during the course of an attack of acute rheumatism, acute lobar pneumonia, or in renal disease.

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[1] *See* footnote on p. 178.

A "primary" pneumococcal peritonitis is occasionally found, usually in girls, the route of infection being apparently through the uterine tube from the genital tract.

Pathological Anatomy. In the earlier stages, there is marked hyperæmia, with serous exudation. Fibrin is formed and is deposited as a fine reticulum on the surface of the intestines, the coils becoming glued together by this exudate. These adhesions are at first soft, and the surfaces in contact are easily separated. If the condition progresses, greater numbers of leucocytes emigrate and in some cases the exudate becomes purulent. The pus is found first round the original focus of infection ; but, if not localised by adhesions, it gravitates to the pelvic cavity or to the right and left lumbar regions. The direction, however, may be influenced by the arrangement of certain peritoneal folds. Thus, effusions resulting from perforation or inflammation of the duodenum, gall-bladder and right lobe of the liver will find their way towards the right kidney ; and those arising in connection with the stomach, towards the spleen. Effusions in connection with the appendix tend to gravitate into the pelvic cavity or are directed upwards alongside the colon towards the right renal or sub-hepatic pouch. The endothelial cells of the peritoneum swell and multiply, and many of them are shed. A certain amount of infiltration with inflammatory products occurs in the subserous layer of the intestine, which becomes swollen and œdematous. Tympanitic distension takes place on account of lack of peristalsis of the muscular coat of the gastro-intestinal canal—" paralytic ileus " (pp. 734, 736 and 757).

The characteristics of the various cells found in the exudate at the different stages are discussed under Inflammation (Chapter II, p. 26 *et seq.*).

If **recovery** takes place, a varying degree of adhesion between neighbouring structures, *e.g.*, the adjacent coils of intestine, or between these and the abdominal wall or some of the other abdominal and pelvic organs, generally remains.

Localised Intraperitoneal Suppuration. Localised inflammation, or localised collections of pus within the peritoneal cavity, may arise from various causes. Such conditions are seen in localised appendix-abscess, round foci of disease in the female pelvic organs, as a result of slow leakage from a gastric or duodenal ulcer, in inflammatory processes around a cancerous growth of the intestine, around diverticula, and in disease of the gall-bladder, bile-ducts, or pancreas. Localised " residual " abscesses may be found in any part of the peritoneal cavity after the subsidence of a widespread peritonitis. Abscesses due to chronic tuberculosis may occur in various situations.

Subphrenic or subdiaphragmatic abscess may arise from almost any intra-abdominal lesion—the commonest, however, being perforation of an ulcer of the stomach or duodenum, suppurative conditions of the liver and its ducts, and appendicitis. In some instances, the focus of infection is above the diaphragm—in the lung or pleura.

Chronic peritonitis may be the sequel of an acute attack, but a slowly-developing peritonitis, with the formation of fibrous adhesions, occurs sometimes in connection with renal disease, or in cancer of the peritoneum. Local thickenings of the capsule of the liver and of the spleen are seen frequently in diseases of these organs, and, very commonly, there are adhesions between them and the parts around. These conditions arise as a result of a proliferative overgrowth of the pre-existing fibrous tissue of the part, caused by chronic irritation—for example, around a gall-bladder containing gall-stones. Chronic peritonitis is probably most frequent in connection with the female generative organs, and often results in adhesions which may cause considerable distortion and perhaps displacement of the organs. It is seen as the result of syphilis, *e.g.*, on the surface of the liver (syphilitic perihepatitis).

Tuberculosis (pp. 64–65, Granulomata).

Tumours :—

Small pedunculated tumour-like masses—sometimes misnamed " lipomata " —and cysts, arising from the appendices epiploicæ, are frequently seen. These are not true tumours, but merely overgrowths of the appendices. Multiple fibromas and sarcomas of retroperitoneal origin occur. Primary tumours of large size, in which a plexiform arrangement of vessels exists—the so-called **angio-sarcomas**—have been recorded. **Endothelioma** of the peritoneum has been reported, but is rare.

Secondary growths of cancer are of common occurrence. Occasionally, widespread miliary nodules are met with. Such **carcinomatosis** is always a secondary manifestation, and is due probably to the cancer-cells being diffused by the fluid in the peritoneal sac, aided by the peristaltic movements of the intestine, the cells entering stomata and being carried to the subperitoneal tissues. The cancer-nodules are frequently flat and firm, and have a pearly lustre. They are, as a rule, especially numerous on the great omentum and on the appendices epiploicæ which are both highly absorbent structures. The abdominal surface of the diaphragm often shows great numbers of the cancer-nodules, and, as the lymphatics of the diaphragm communicate freely with those of the pleura, spread to the latter structure frequently takes place. Such secondary deposits arise usually from direct spread from carcinoma of stomach or intestine. If the tumour is of the " colloid " type, the peritoneum may become a mass of " mucinoid " or myxomatous nodules. Rupture of a mucocele of appendix (pp. 746–7), or of a cystadenoma of ovary, may lead to an accumulation of mucus and—in the case of the ovarian growth—to the production of small secondary cysts in the peritoneum, matting together neighbouring coils of intestine. The condition is sometimes called " pseudomyxoma peritonei."

Chylous cysts, usually small, due to obstruction and distension of the lacteals, are not infrequently seen on the surface of the intestine and mesentery.

Parasites :—

Hydatid cysts (pp. 400–405 and Fig. 221, p. 401, and Fig. 444, p. 784) are the only important animal parasites of the peritoneum. They may be primary in the omentum or mesentery, or secondary to rupture of a cyst in the liver. They are frequently multiple and, clinically, the condition may simulate tuberculous peritonitis.

CHAPTER XXII

DISEASES OF THE LIVER

Introductory. Before studying the pathological changes which occur in the liver as the result of disease, the reader should recall the main facts in connection with the anatomical and histological structure and with the physiology of the organ. Here we can refer briefly to only a few of the more important of these features.

The liver has a double circulation, portal and hepatic, with anastomoses between these at the periphery of the lobules. The portal stream is not homogeneous, that going to the left side of the liver is mainly from the spleen and stomach, that to the right side is mainly from the intestines. These differences help in the understanding of the distribution of lesions in the liver. The liver is concerned with the excretion of bile, but the pigment, bilirubin, is formed only partly in the liver—by its reticulo-endothelial system. In the fœtus, the liver is a hæmopoietic organ, and this function may reappear in the adult under certain pathological conditions. The various chemical processes—urea and amino-acid formation : glycogen-formation : fat-metabolism : fibrinogen-formation, etc., may be interfered with when liver-tissue is damaged. Various clinical tests have been devised in the endeavour to estimate the functional capacity of the organ, but the difficulty of estimating the value of these tests in actual practice is that the liver has an immense functional reserve capacity, so that, although much tissue is destroyed, the remainder can still carry on satisfactorily. In addition, an ability for regeneration is a marked feature of liver-tissue and may rapidly restore to full functional capacity an extensively-damaged organ.

MALPOSITIONS and MALFORMATIONS :—

The liver may be transposed in cases of general transposition of the viscera (Fig. 251, p. 447). Abnormalities in the arrangement of the lobes and the presence of accessory lobes and sulci are of anatomical, rather than pathological, interest, though a downward elongation of or projection from the right lobe—a Riedel's lobe—may be of clinical interest, as it may be mistaken for a tumour of the colon or an enlarged kidney. Displacements are frequently observed, the liver being displaced either upwards or downwards, and the suspensory ligament often elongated. The hepatic artery may be doubled ; or the ductus venosus remain patent.

ACQUIRED DEFORMITIES and DISPLACEMENTS, such as those produced by the pressure of tumours or of fluid accumulations, are common. Pressure on the lower part of the thorax, such as is brought about by tight-lacing or by prolonged wearing of a tight belt is said to cause a flattening of the liver and the production of transverse grooves, especially in the right lobe. At the bottom of such grooves, the capsule is thickened, and there is considerable atrophy of the liver-tissue. These grooves may be well-defined, and so-called " artificial lobes " of the liver be produced, these lobes being, in extreme cases, attached to the main part of the organ by only the thickened capsule, fibrous tissue, and vessels (Fig. 421). Depressions corresponding with the lines of the ribs are frequently seen. Vertical or antero-posterior (" sagittal ") sulci on the upper surface of the liver are due to plications of the diaphragm (*see* Fig. 421A on p. 790).

Capsular Changes. Following acute inflammation such as peritonitis, there may be some thickening and adhesions of the capsule to the diaphragm or adjacent organs. In chronic inflammatory conditions such as syphilis and chronic tuberculosis, localised capsular thickenings are sometimes found. Apart from these obvious infective conditions, thickening is also frequently associated with cirrhosis of the liver, especially in cases with long-continued ascites.

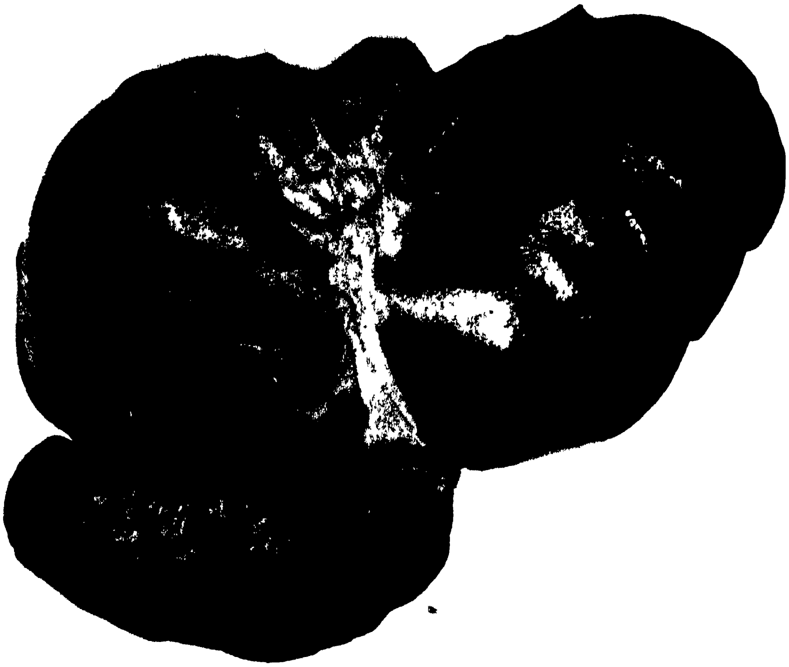

FIG. 421. *Liver*, showing atrophic sulci, the result of pressure.

REGENERATIVE CHANGES IN THE LIVER[1]:—

It has been shown by experiment that, if one-half or even three-quarters of the liver of an animal be removed, repair takes place very rapidly, and that the organ may regain its ordinary size—the newly-formed tissue being, in the main, indistinguishable from normal liver-tissue and able to function as such. Mitotic figures are easily demonstrated in the newly-formed tissue, and there seems to be no reason to doubt that the repair takes place by a proliferation of liver-cells. The part played by the bile-ducts in this new formation is more uncertain, but it seems probable that the cells lining the terminal bile-ducts may be transformed, at any rate in certain areas—though it may be, imperfectly—into secreting hepatic cells. Regeneration of liver-cells is retarded, or even prevented, if the portal circulation is inefficient or obstructed.

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[1] Lindsay Milne, Thesis for Degree of M.D., University of Edinburgh, 1908 ; and *Brit. Med. Jour.*, 1908, ii, 1169. Turnbull and Worthington, 1908, *Archives of Pathological Institute*, London Hospital, **2**, 35 *et seq.* (Older references are given in both of these communications.) See also *Archives of Pathology*, 1929, **7**, 955 ; 1931, **12**, 186 1932, **14**, 491.

These regenerative changes are common in pathological conditions of the liver, especially in cases in which there is any destruction of the secreting-cells of the organ. Thus, in acute and subacute "liver-atrophy," cirrhosis, chronic venous congestion, abscess-formation, cancer, etc., there may be seen, microscopically, irregular areas in which the liver-cells stain somewhat intensely, show an atypical arrangement, are irregular in size and shape, and exhibit active proliferative changes. Mitotic figures in the proliferating cells may be found. These are undoubtedly regeneration-areas, and are regarded as compensatory in nature. The new bile-ducts, which occur apparently in excess in some of the pathological conditions mentioned above, arise by proliferation from pre-existing bile-capillaries—which may show mitotic figures—though some authors still hold that they arise from liver-cells. Lindsay Milne suggests

FIG. 422. *Multilobular Cirrhosis of the Liver,* with large, projecting, comparatively smooth nodules. These latter are areas of compensatory or complementary hypertrophy.

that the appearances taken to indicate the occurrence of proliferation of bile-ducts are really due to the flattened epithelial cells lining minute pre-existing bile-channels becoming swollen and cubical in form and thus more apparent. This change in the small bile-ducts may be regarded as analogous to that seen in the cells lining the pulmonary alveoli in chronic interstitial fibrosis in the lung.

CIRCULATORY DISTURBANCES :—

(*a*) Pale (" **ischæmic** ") patches are frequently seen on the surface or in the substance of the liver, and are merely the result of pressure by the ribs or by neighbouring viscera—usually after death.

(*b*) **Acute congestion** occurs in various toxic and septicæmic diseases. As cloudy swelling (p. 190) supervenes, the previously congested vessels become emptied of their blood by the pressure of the swollen liver-cells.

(*c*) **Chronic venous congestion** results from obstruction to the circulation of the liver (p. 151 *et passim*).

(*d*) **Embolism and Thrombosis (Pylethrombosis) of the Portal Vein.** Though these conditions may arise as a result of pressure on or invasion of the vein by tumours, etc., they are usually the result of the detachment of portions of an infective thrombus, or the direct extension of this thrombus from one of the radicles of the vein—especially a mesenteric vein—in cases of septic enteritis, appendicitis, inflamed hæmorrhoids, or other infective conditions in areas from which the portal blood comes. The blocking of the vein may cause complete necrosis of the central two-thirds of the lobules, though in some cases comparatively little damage to the liver-tissue results—the nutrition of the cells, especially those at the periphery of the lobules, being maintained by the hepatic artery. Even without necrosis, the circulatory changes in the involved area result in the production of a dark-red area resembling a red infarct. If the condition becomes chronic, there is usually abundant proliferation of the connective tissue and perhaps leucocyte-infiltration of the affected portal tracts. The sepsis, however, not infrequently extends into the interlobular and other branches of the vein, and these may become distended and infected, with the production of large irregular suppurative areas (pylephlebitis) and considerable destruction of the liver-tissue (p. 779). The obstruction of the vein sometimes brings about a dilatation of all its radicles in the abdominal viscera, and produces a condition of passive hyperæmia with ascites. If the thrombosis spreads backwards so as to involve any of the great tributaries of the portal vein, serious pathological changes may occur in the organs which they drain.

On account of the free anastomosing channels and of the fact that the liver-tissue is nourished largely by the portal vessels, embolism or thrombosis of branches of the hepatic artery usually produces little change of importance [1]—unless the plug be of an infective nature, in which case abscess-formation may result—but hæmorrhagic infarcts of the liver have been described, and in these cases there has usually been thrombosis in many branches both of the hepatic artery and of the portal vein, or thrombosis in the portal vein with extensive degenerative (endarteritis obliterans), and therefore obstructive, changes in the hepatic artery.

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[1] Lindsay Milne (*loc. cit.*) finds that experimental ligature of the portal vein in rabbits, cats and dogs produces rapid necrosis of the central two-thirds of the lobules ; whilst ligature of the hepatic artery produces no visible effect.

RETROGRESSIVE CHANGES IN THE LIVER:—

In studying the retrogressive processes in the liver, it must be borne in mind that changes due to decomposition take place very rapidly in the organ. Local alterations of colour are common—a bluish-black discoloration (**pseudomelanosis**) appearing, especially where the liver is in contact with the transverse colon : and yellowish or pale "**ischæmic**" **patches** showing, as a result of the pressure of the ribs, etc. **Gas-formation** may occur after death, and is seen in its most pronounced form as an extensive honeycombing of the liver which results occasionally from infection with *Clostridium welchii* (*see* pp. 236–7, Fig. 111 : and p. 784). There seems very little doubt, however, that, though the most active growth of this organism takes place after death, yet there are cases in which the "emphysematous" condition of the liver produced by it is of ante-mortem occurrence, *e.g.*, in cases of gas-gangrene. The pseudocysts produced in this way are simply air- or gas-spaces without liquid contents. Their walls, formed directly of liver-tissue and without lining membrane, are dry and smooth, and the gas-producing organisms may be found microscopically in large numbers in the walls and adjacent liver-tissue.

(*a*) **ATROPHY** of the liver-cells supervenes in old age, and also in diseases which, either as a result of general toxic poisoning, or merely following interference with the absorption of food, cause general emaciation. Thus, the condition is seen sometimes to a marked degree in cases of phthisis, and in cancer of the stomach.

Local Atrophy may result from pressure by tumours in the liver, by dilated capillaries in chronic venous congestion, by dilated hepatic veins, especially if near the surface of the organ, or by the swollen capillary walls in amyloid degeneration. Obstruction of the common bile-duct, by causing dilatation of its tributaries, may also bring about pressure-atrophy of the liver-cells. **Microscopically,** the liver-cells of the affected part become distorted, decreased in size, and usually pigmented. At later periods, they break down and disappear.

(*b*) **CLOUDY SWELLING** of the liver-cells occurs in connection with all acute bacterial and toxic diseases (Chapter VIII, p. 190).

(*c*) **FATTY CHANGES** are common (Chapter VIII, p. 194 ; Plate IX, Figs. 1 and 3, p. 200).

(*d*) **AMYLOID DEGENERATION** in the liver is always associated with amyloid degeneration in the spleen and the kidney, and perhaps also in other organs (Chapter VIII, p. 210, and Plate X, Fig. 3, p. 210).

(*e*) **PIGMENTARY CHANGES.**—An increased amount of pigment occurs in the liver-cells in various diseased conditions (Chapter VIII, p. 218 *et seq.*).

(*f*) **GLYCOGENOUS INFILTRATION** occurs, but has been sufficiently referred to in Chapter VIII, p. 207.

(*g*) **FOCAL NECROSIS** in the liver is dealt with in Chapter IX, p. 246.

(*h*) **"ACUTE LIVER-ATROPHY** "(or "**Acute Yellow Atrophy** "). This condition is better described as an acute **necrosis** with rapid **lysis** of the damaged cells, than as an " atrophy." The condition is widespread throughout the liver, the special cells of which appear to " melt away " under the action of the unknown

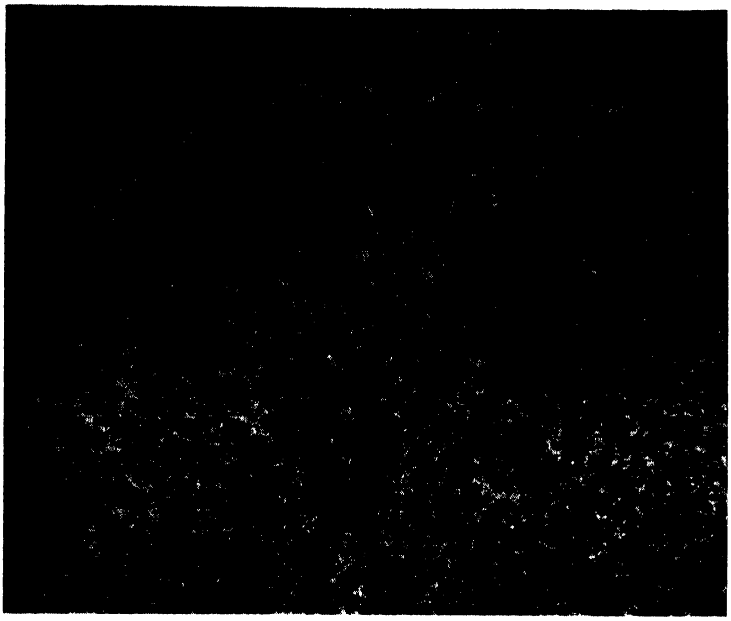

FIG. 423. "Acute liver-atrophy." Most of the section is occupied by necrotic debris of liver ; only a few liver-cells have survived—seen as a darker zone extending towards top right. No bile-duct proliferation is yet seen. Hæmatoxylin and eosin. × 125.

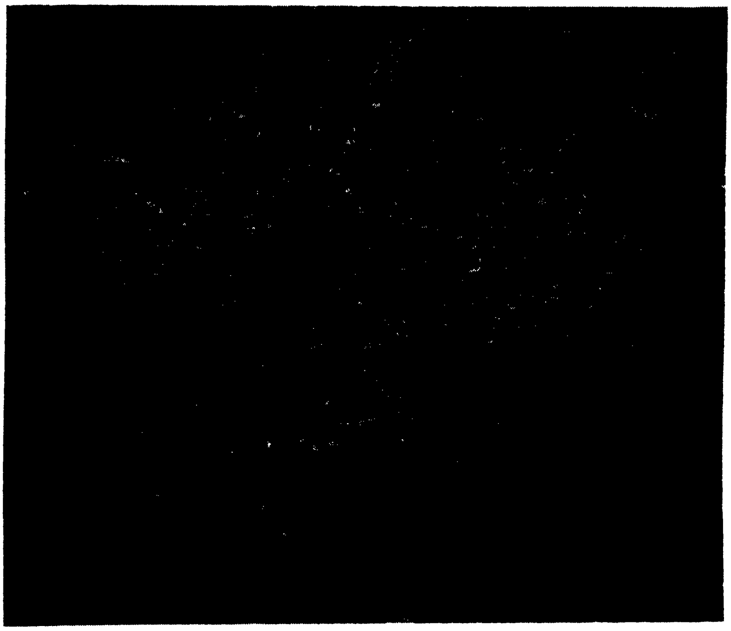

FIG. 424. "Subacute liver-atrophy." At top left is an area of hyperplastic liver, the central area is occupied by many small darkly-stained, proliferated bile-ducts in a paler matrix of fibrosis. Hæmatoxylin and eosin. × 75.

damaging agent. The disease may occur at any age and in either sex. It is frequently said to be common in pregnancy or during the puerperium, but this is due to the inclusion of somewhat similar, but not identical, lesions occurring in the " toxæmias " at these epochs (see p. 775 for discussion of ætiology).

Clinically, there is usually a period of a week or two of mild gastro-intestinal disturbance, followed abruptly by a severe intoxication with prostration, progressive jaundice, delirium and coma. There is usually a moderate polymorphonuclear leucocytosis at this period. The urine is scanty and contains bile-pigment and amino-acids (leucine and tyrosine crystals may be found). Death occurs usually in one or two weeks from the onset of serious symptoms.

Morbid Anatomy. Clinically, in the early stages, the liver appears to be enlarged, but it soon rapidly diminishes in size until—as seen after death—it is uniformly small, its capsule wrinkled as if too big for its contents, and its colour red, or a dirty reddish-yellow. On section, the appearances vary, depending upon the extent of the destruction and the duration of the illness. It may be dark red, or mottled red and dirty yellow. The yellowish areas may be friable but, as a whole, the organ has an elastic firmness. The gall-bladder shows no unusual feature and may contain bile, or only bile-stained mucus.

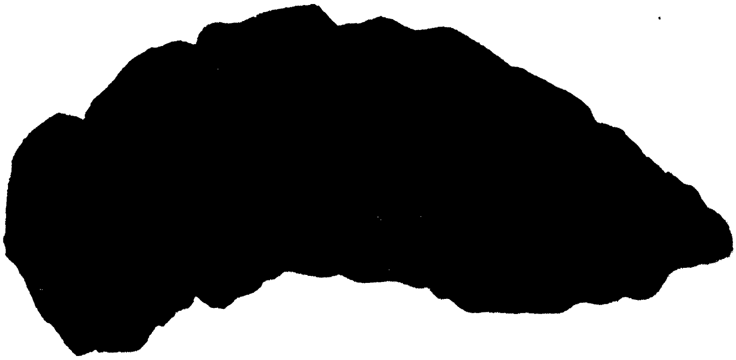

FIG. 425. " Subacute atrophy " of liver. Appearance on section. The lighter areas consist of hyperplastic liver-tissue, the darker of fibrous tissue.

Microscopically (Fig. 423), there is extensive disintegration and disappearance of the liver-cells with, here and there, liver-cells in groups or singly, showing all stages of damage—some granular, some fatty. Between the surviving liver-cells, and in place of those which have disappeared, the sinusoids are congested (giving the red colour seen macroscopically), there may be slight fibroblastic proliferation and there are many phagocytic cells, and much cell-debris and bile-pigment. The bile-ducts are not necrosed; they may appear unduly prominent and may be even proliferating.

(*i*) "**SUBACUTE LIVER-ATROPHY**" is a lesser degree of the same condition. Clinically, the symptoms are less urgent but more prolonged, with persistent jaundice; and death may not occur for weeks, or even months. Indeed, recovery may take place in the less severe cases. Owing to the extensive destruction of liver-cells, those surviving proliferate to compensate for the loss, much in the same way that regeneration occurs in an experimental animal following removal of large portions of liver-substance. These regenerating areas stand out as light-yellow nodules projecting from the surface of a red groundwork composed of the framework of the destroyed areas, plus fibrous overgrowth. The bile-ducts also proliferate and are seen in great numbers in the fibrous areas and at the periphery of the hyperplastic liver-nodules (Fig. 424). If recovery takes place, the liver is found diminished in size but very coarsely nodular. To this condition the term **multiple nodular hyperplasia** is sometimes given (Fig. 425). It is, indeed, a form of " cirrhosis " (p. 771 *et seq.*).

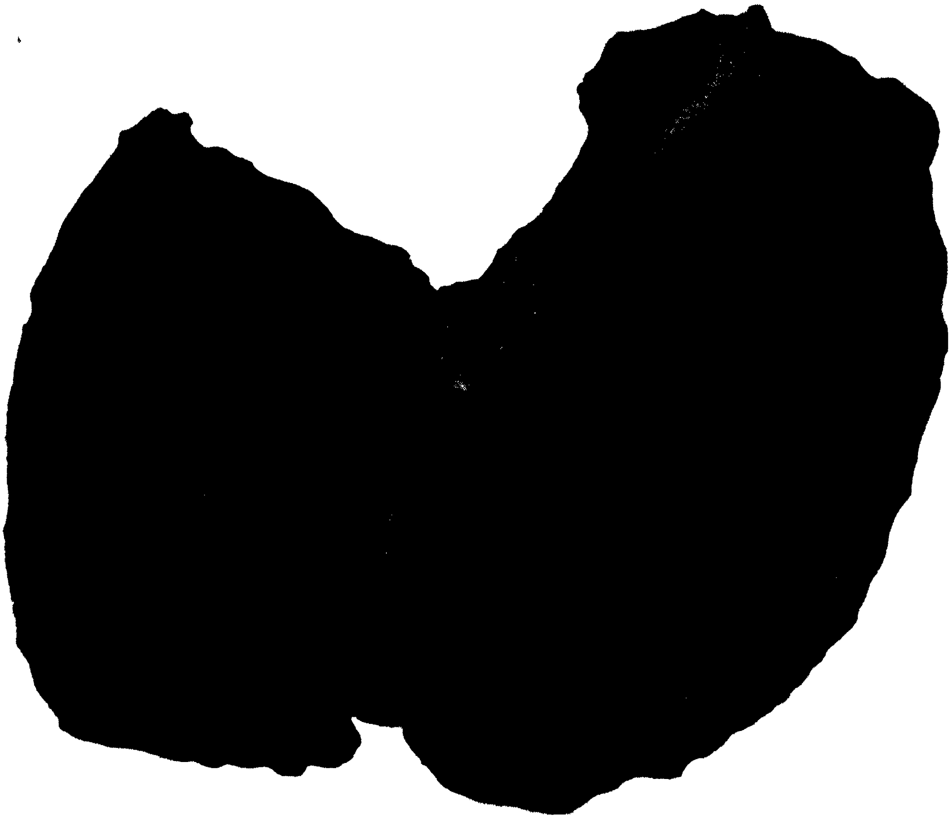

FIG 426. " Subacute atrophy " of liver (multiple nodular hyperplasia). This superficial view shows the coarsely nodular surface.

(*k*) " **CATARRHAL JAUNDICE**." This condition was considered by Virchow to be a catarrhal condition of the large and smaller bile-ducts, leading to their obstruction from swelling of the mucosa and accumulation of mucus. As recovery from the condition usually occurs, it has not been possible, until recently, to study the liver-changes. Gaskell [1] had the opportunity of studying a case which died, from another cause, on the third day of the disease, and he confirmed the findings of Schrumpf (1932) who described the appearances in the liver as those of " acute yellow atrophy in miniature." These observers found no indication of bile-duct catarrh, but they did find acute degeneration of

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[1] *Jour. of Path. and Bact.*, 1933, **36**, 257.

FIGS. 427. 428. 429. The Liver in eclamps

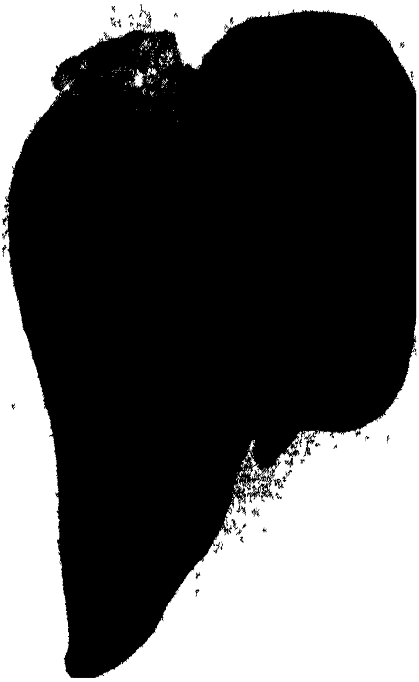

FIG. 427. The outer surface is mottled wit dark areas of hæmorrhage and pale areas liver, normal or necrosed

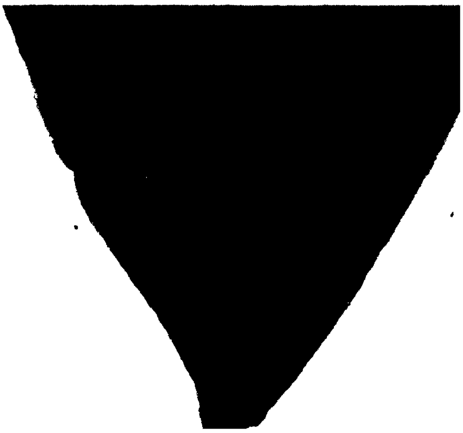

FIG. 428. The cut surface shows simila mottling; much of the pale tissue i necrotic

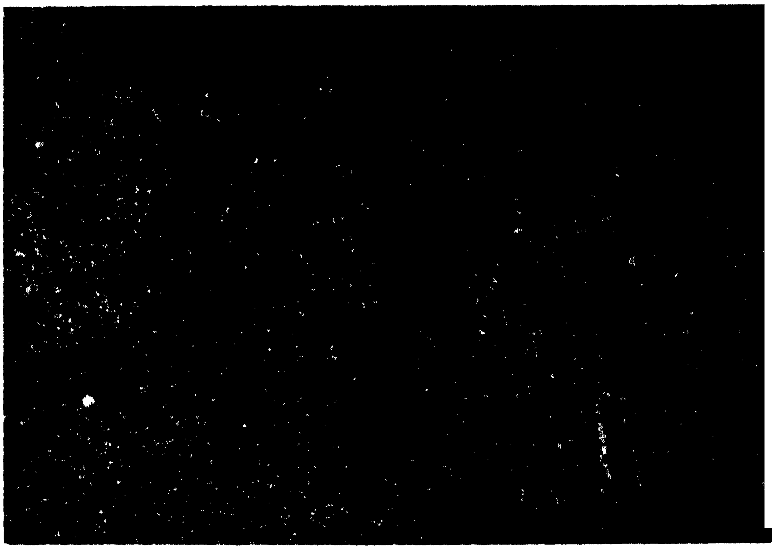

FIG. 429. To the left is necrotic liver-tissue; in the centre are congested sinusoids and scattered hæmorrhages interspersed with necrotic liver-cells. To the right is a portion of undamaged liver-lobule. Hæmatoxylin and eosin. × 90.

liver-cells. Occasionally this disease may progress and end with all the appearances of acute liver-atrophy. Epidemics of " catarrhal jaundice " may occur, and, on the Continent of Europe, fatal cases have been not infrequent.[1]

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[1] *See* Findlay and Dunlop, *Brit. Med. Jour.*, 1932, i, 652; and Findlay, Dunlop and Brown, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1931, **25**, 7.

Catarrhal jaundice is infective and, although the infective agent has not yet been identified, the possibility of a virus must be considered.

In **Weil's Disease (Spirochætosis icterohæmorrhagica)**, or **febrile jaundice**, the changes in the liver are similar to those of "catarrhal jaundice." Here, however, the spirochæte, or *Leptospira*, may, under suitable conditions, be demonstrated in the liver and elsewhere (p. 374).

Yellow Fever, in which deep jaundice is present, is also associated with scattered necrosis of liver-cells, usually at the periphery of lobules. There is also marked fatty change in this infection.

(*l*) Other examples of liver-necrosis. In the so-called "**Toxæmias of Pregnancy**" necrosis is frequently present. This may be confined mainly to the centre of the lobule ("central necrosis") though its distribution varies. In **Eclampsia** (Figs. 427–8–9), in addition to irregular necrosis there is usually hæmorrhage from endothelial damage. Many severe infections may cause "focal" (p. 246), or more extensive, areas of necrosis. A number of chemical substances are responsible for liver-necrosis. Phosphorus, besides producing acute fatty changes, may kill the cells. Chloroform may act similarly. Other chemicals, such as carbon tetrachloride, tetrachlorethane, salvarsan (and allied arsenical preparations), trinitrotoluol (or trinitrotoluene), etc., have been found to produce damage ranging from fatty change, "hydropic degeneration," to complete necrosis. Poisoning with **trinitrotoluol** (T.N.T.) [1] is deserving of mention, as it was responsible for a number of fatal cases in munition-workers during the War of 1914–18 (*see also* pp. 245, 664 and 777). The liver-lesions resemble so closely those of "acute" and "subacute liver-atrophy" that the same descriptions would serve for both.

CHRONIC INTERSTITIAL HEPATITIS (CIRRHOSIS) [2] :—

This title covers a group of conditions in which the essential features are overgrowth of fibrous tissue, loss of some liver-cell tissue and hyperplasia of the remainder. A number of different forms of cirrhosis have been described and classified, but many of these forms are but variants of the same process and depend on factors such as the extent of the initial damage and resulting repair, the route by which the damaging agent reaches the liver, the acuteness or chronicity of the process, and the stage of development of the disease at which the opportunity of examining the liver has arisen.

We have already seen how a "subacute atrophy" may lead to the production of a nodular liver, "multiple nodular hyperplasia," which is in reality nothing but a gross form of cirrhosis.

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[1] T.N.T., either pure or compounded with ammonium nitrate (amatol or ammonal), may be absorbed through the skin or through the digestive tract, or by inhalation of its fumes or dust. It may cause dermatitis, neuro-vascular conditions, gastro-intestinal disturbances (especially gastritis and constipation), and occasionally a very fatal form of anæmia (aplastic anæmia), as well as the liver-degeneration or "toxic jaundice" described above.

[2] "Cirrhosis," from Greek, κιρρός, *kirrhos*, orange-tawny, a colour intermediate between πυρρός, *pyrrhos*, flame-coloured or yellowish-red, and ξανθός, *xanthos* (whence "xanthochromia" —*see* p. 963) yellow, perhaps with a slight tinge of red in it.

Common Cirrhosis (multilobular or " polylobular," cirrhosis : " hobnail," or portal cirrhosis, coarse atrophic cirrhosis of Laennec, alcoholic cirrhosis or " gin-drinker's liver "). Fine and " hypertrophic " cirrhosis, etc. The various synonyms of this condition are either purely descriptive or designed to indicate the supposed route and cause of the damage.

The condition is slowly produced, it may be slowly progressive, or be arrested at any stage. It may have caused no obvious clinical symptoms and be discovered accidentally at post-mortem; or the symptoms may be due entirely to interference with the portal circulation in the liver.

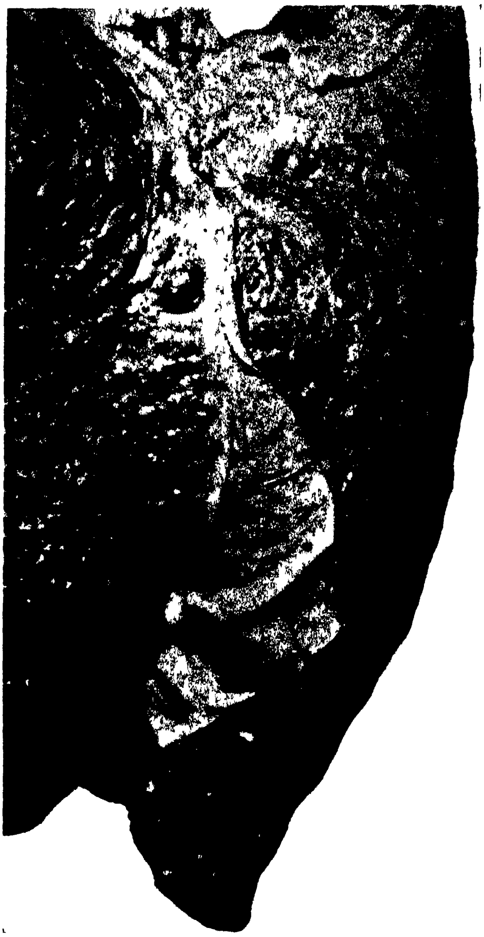

FIG. 430. Common or multilobular cirrhosis of the liver, showing " hobnail " appearance of the surface.

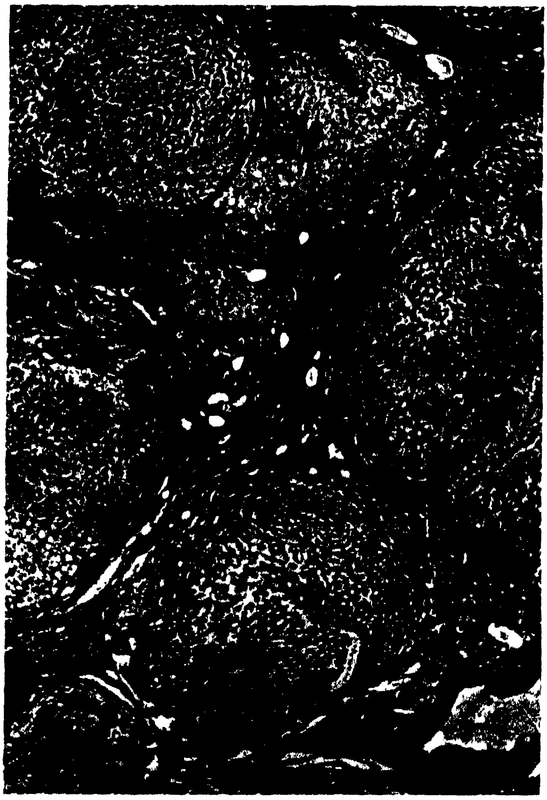

FIG. 431. Common or multilobular cirrhosis of the liver. Van Gieson's stain. ×25.

In what may be termed the more **acute** forms, there may be seen damaged liver-cells, fatty changes, and jaundice, and, in such forms the liver is enlarged, the surface smooth or only finely granular, the fibrosis is cellular and encloses small areas, or single lobules, of liver-tissue—hence the terms " fine " and " hypertrophic " cirrhosis. In this group may be placed the **hypertrophic cirrhosis of Hanot**, which is usually described as a "fine cirrhosis with jaundice," though some examples of this rather vague type may be of the biliary obstructive type (*see* opposite, and p. 774). In this group, the bile-ducts usually show proliferation, and are seen ramifying in the fibro-cellular tissue.

In the more **chronic** forms, which are the commonest, the liver is usually reduced in size (atrophic cirrhosis), irregularly nodular on the surface (hence " hobnail " and " coarse ") and firm on section. The fibrous tissue varies in amount, but is usually dense and often in thick strands. The size and nature of the areas of included liver also vary—usually several lobules are incorporated in the nodule (hence " multilobular "). On **microscopical examination** of the nodule (Fig. 431), it may be seen to consist of an atypically arranged mass of liver-cells, or several lobules may form it, but these lobules are usually distorted, the original " central " veins being displaced towards the periphery owing to the irregular incidence of the damage and the resulting regeneration and hyperplasia. Bile-ducts are infrequent in the fibrous tissue, their frequency varying inversely with the density of the fibrous overgrowth.

Secondary changes may accompany or be superadded to the cirrhosis, viz., fatty change, or even areas of necrosis, in the liver-cells. The distortion of the structure of the liver by irregular damage, irregular fibrosis and hyperplasia, leads to various degrees of vascular obstruction in the portal area. This has been well demonstrated by means of celloidin injection.[1]

In certain syndromes, *e.g.* Wilson's disease, cirrhosis is associated with changes in the central nervous system, more particularly the basal ganglia (p. 1070).

Portal Obstruction. Frequently this is the only disturbance that indicates cirrhosis of the liver clinically. In the cirrhotic liver, the portal vessels are reduced in number and are given off at irregular angles as compared with the condition in the normal liver. The difference recalls that between the atrophic granular kidney and the normal kidney. Microscopically, in such a liver, there may be great engorgement of the venules in the fibrous tissue and in the sinusoids. The obstruction leads to **ascites**, often of very persistent character, requiring repeated paracentesis to remove the fluid which collects. The collaterals between the portal and systemic circulations open up and even a varicose condition of the veins may occur at these points, viz., at the lower end of the œsophagus or cardiac end of stomach, along the line of the diaphragm, around the umbilicus (giving the " caput medusæ "), in the hæmorrhoidal veins, etc. Rupture of such vessels in œsophagus or stomach is not uncommon and may cause a fatal hæmorrhage. The spleen is engorged and enlarged.

Primary liver-cell carcinoma (Figs. 440–2, pp. 781–2) may supervene on a cirrhosis and, owing to invasion of portal veins by tumour, an even greater portal block is produced, with still greater, or more rapidly increasing, ascites.

Biliary Cirrhosis. This is sometimes called **obstructive** biliary cirrhosis, as it is caused by some form of obstruction to the outflow of bile. It may be found at birth in cases of **congenital** obliteration of the bile-ducts. More commonly it results from such factors as calculi in the common bile-duct or main bile-ducts, carcinoma in these or in the duodenum or head of the pancreas, enlarged lymph-nodes at the hilum of the liver, etc. The retained bile, acting as an irritant, damages the liver-cells and they are replaced by overgrowth of fibrous tissue. The liver is usually enlarged, deeply jaundiced, and smooth or finely granular on the surface. On section, the cirrhosis is usually of the fine unilobular (or so-called " monolobular ") variety. The bile-ducts are dilated and filled with bile. **Microscopically** (Fig. 434, p. 776), there is a cellular and peri-lobular fibrosis in which are embedded many small bile-ducts and a variable number of inflammatory cells, mainly lymphocytes and large mononuclears. Inspissated bile can be seen in the bile-ducts, in Kupffer's cells, and even in liver-cells. A variable degree of degenerative change is present in the surviving liver-cells. If the condition is of long standing there may be liver-cell hyperplasia and denser fibrosis, giving a " coarse " cirrhosis and resembling the " portal " type, accompanied by deep jaundice and bile-duct dilatation.

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[1] McIndoe, *Arch. Path.*, 1928, **5**, 23.

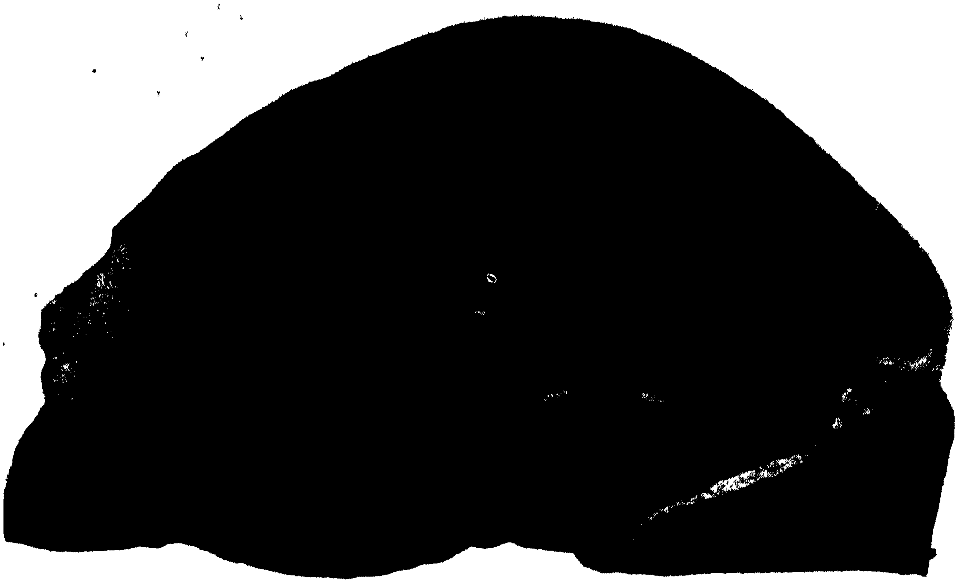


FIG. 432. *Liver in hæmochromatosis.* The appearance on section is that of a regularly distributed unilobular cirrhosis, each lobule being clearly demarcated by fibrous tissue.

Rarer Forms of Cirrhosis. Hæmochromatosis (Fig. 432) (*see also* pp. 227, 793, 804 and 1070) is a form of " fine " cirrhosis with an abundant accumulation of iron-containing and iron-free pigment in the liver-cells and in phagocytes. Its ætiology is obscure.

Malarial Cirrhosis is usually described as being unilobular in type, with the liver small and irregular in appearance, resembling the condition seen in " alcoholic " cirrhosis. By some authors, this form of cirrhosis, which undoubtedly occurs in certain cases of malaria (p. 382), is regarded as independent of, and not caused by, the continued malarial attacks. It is practically impossible, in any given case, to exclude all the other possible and well-recognised causes of cirrhosis and therefore the actual proof of the existence of a definite "malarial cirrhosis" cannot as yet be regarded as definitely established.

Cirrhosis due to Kala-Azar was described, in 1908, by Leonard Rogers, who found varying degrees of the condition in about one quarter of all cases of this disease. In a series of adult cases of chronic kala-azar, investigated by Nattau-Larrier in India, it was found that the hepatic fibrosis might be either insular or diffuse, the latter form being a fine peri-capillary fibrosis, closely resembling the intercellular, unicellular (or so-called "monocellular") cirrhosis of congenital syphilis (pp. 85–6 and Fig. 48). The protozoal parasites may be demonstrated in the fibrous tissue of the lesions.

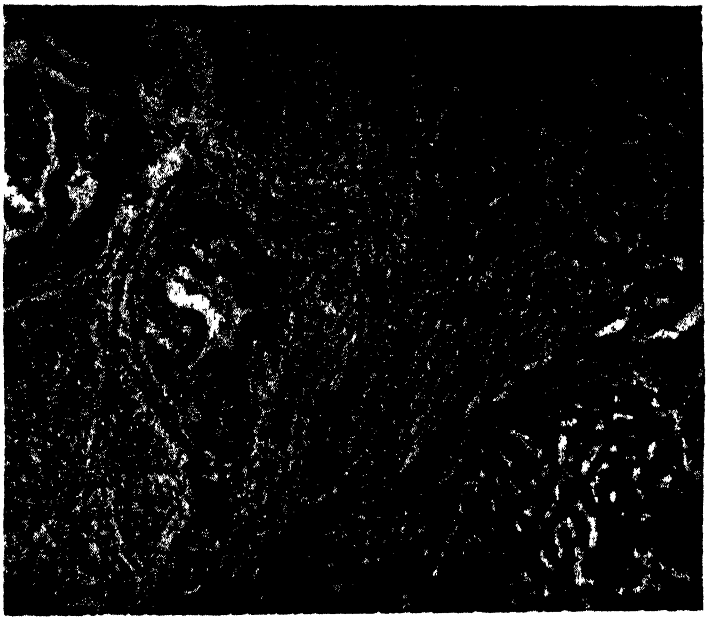


FIG. 433. *Bilharzial cirrhosis.* A portion of portal tract is shown with great excess of fibrous tissue, aggregated especially around bilharzial (*Schistosoma*) ova. Proliferated bile-ducts lie to the left and a lobule of liver to lower right. Hæmatoxylin and eosin. × 65.

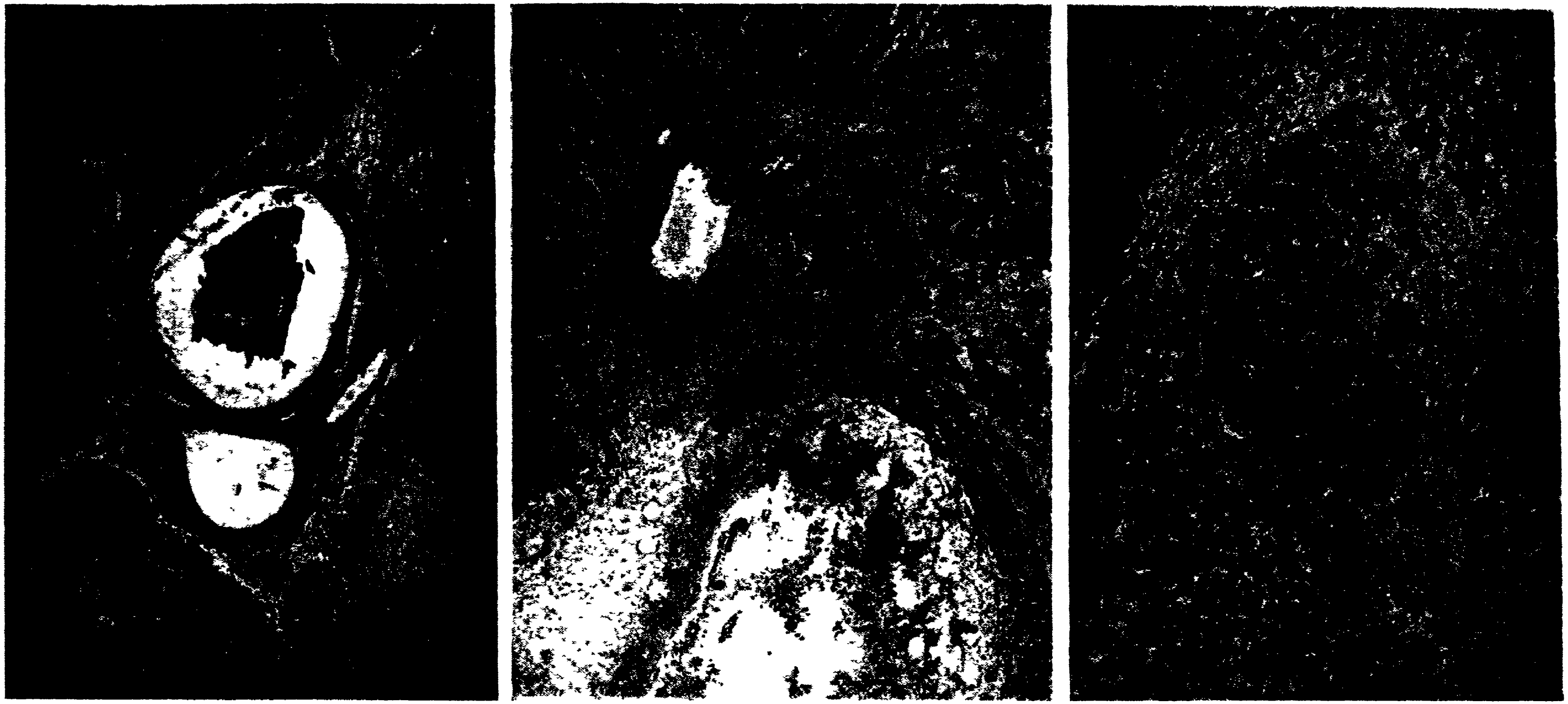
Cirrhosis due to Trematode (Fluke-Worm) Infestation (Fig. 433). In man, the spined ova of *Schistosoma hœmatobium* and *S. mansoni* may be deposited in the portal tracts and excite much fibrosis around them. The ova can be recognised easily in the fibrous tissue and occasionally adult worms also are present in the portal veins in the liver (Fig. 208, p. 390 and *cf.* p. 391). The adult forms of *S. japonicum* may similarly occur in the portal veins in the liver and produce local fibrosis around. Rarely in man, but commonly in sheep and cattle, *Fasciola hepatica* (p. 384) may produce similar changes.

Ætiology and Mechanism of Production of Hepatic Necrosis and Cirrhosis.

In the foregoing descriptions of different lesions, the factors common to all have been the destruction of liver-cells, their replacement by fibrous tissue, regeneration of new liver-tissue by the survivors: proliferation of the bile-ducts and their relative immunity from damage.

Many attempts have been made to reproduce experimentally the acute

FIG. 434. *Obstructive biliary cirrhosis.*



(A) × 28.

In the centre is a dilated small bile-duct filled with dark inspissated bile. A pale area of recent necrosis is seen to the lower right.

(B) × 75.

Another area where there is recent necrosis of liver-cells—below: with fibrosis in a portal tract—upper central area—in which is a small bile-duct filled with bile and debris.

(C) × 75.

Another area. Fibrous strands in which are small proliferated bile-ducts—irregularly dividing up the columns of liver-cells.

and chronic forms of damage, and many substances have been used for this purpose.

In some instances, a combination of factors acts more effectively in producing a liver-lesion than each of the factors individually ; thus chloroform alone in toxic amounts may produce only fatty change : or scattered small patches of necrosis ; chloroform *plus* infection by bacteria may produce severe necrotic lesions and a fibroblastic reaction. Also factors such as starvation, lack of glucose or excess of fat, may favour the damaging-action of various agents upon the liver-cells. Of experimental substances, manganese is perhaps the one which can in animals produce lesions most resembling the human lesions, acute and chronic. As shown by Findlay,[1] and Hurst and Hurst,[2] large doses, in the rabbit or guineapig, produced a fatal result with extensive areas of acute necrosis of the liver-cells, but little or no obvious damage to the bile-duct epithelium. Smaller doses, repeated at intervals, did not kill the animals, but caused scattered small areas of necrosis of liver-cells, followed later by fibrosis, thus presenting a picture resembling that seen in human cirrhosis.

Cameron and his co-workers [3] have investigated the experimental effects of many chemical substances of the aliphatic and aromatic series and find that many of these produce liver-damage from toxic action on the liver-cells ; even inhalation, *e.g.*, of *o*-dichlorbenzene in low concentration produced scattered areas of necrosis.

These workers have also shown that necrotic hepatic cells may be absorbed and leave no subsequent fibrous scar in the liver ; or, if a scar should form, it may be absorbed later and no permanent fibrosis remain. If, however, the liver is exposed to repeated injuries, the destroyed liver-cells become replaced by permanent scar-tissue.

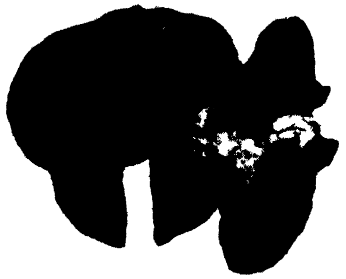


FIG. 435. *Liver of rat.* Experimental cirrhosis due to repeated administration of carbon tetrachloride. The surface is finely nodular. (A portion has been removed from a lower lobule for histological examination.)

The various substances used experimentally in animals to produce liver-damage, with or without subsequent cirrhosis, are not likely to be causal factors in the human subject. The older view that liver-damage resulted from absorption of toxins of various kinds from the alimentary tract is reasonable enough, but the difficulty has been to demonstrate the actual noxious agent in any given case.

The findings in T.N.T. poisoning, to which reference is made on pp. 245, 664 and 771, certainly indicate that absorption of this substance into the circulation can result in severe liver-destruction. Alcohol, especially in the form of "spirits," and more particularly gin, has been frequently accused as the causal agent ("gin-drinker's liver"), but there is no constant, or even frequent, association between chronic alcoholism and cirrhosis. Any action alcohol may have must be indirect or perhaps in association with bacterial toxins—as in the experimental finding with chloroform *plus* bacteria. Moreover, cirrhosis appears not infrequently to have a familial or hereditary element of predisposition in its ætiology (p. 1070).

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[1] *Brit. Jour. Exper. Path.*, 1924, **5,** 92.

[2] *Jour. Path. and Bact.*, 1925, **31,** 303.

[3] *Jour. Path. and Bact.*, 1937, **44,** 281, 297.

Several conclusions emerge from a study of human cases and experimental work :—

(*a*) Many different agents can cause necrosis of liver-cells, but the bile-duct epithelium is relatively unaffected.

(*b*) If necrosis is extensive, death of the patient may result in the acute or subacute phase.

(*c*) Recovery may occur where liver-damage is less extensive and be characterised by replacement of the necrosed liver-cells by fibrous tissue and by compensatory hyperplasia of the surviving liver-cells.

(*d*) It is still doubtful whether liver-necrosis alone can excite fibrous replacement, or whether the connective-tissue cells may not require to be damaged, or at least irritated, simultaneously. Certainly, loss of part of the liver-parenchyma leads to compensatory overgrowth of liver-cells. These appear to arise from pre-existing liver-cells rather than from bile-duct cells, although new bile-ducts are also formed and coaptation between these and liver-cells occurs.

(*e*) In the case of infestation with *Schistosoma* (*Bilharzia*), the primary change appears to be a fibrosis in the portal tracts excited by the worms or their ova in these areas.

"INFLAMMATION OF THE LIVER" :—

Acute inflammatory changes in the liver, apart from abscess-formation, are said to occur commonly in tropical countries, and especially in cases of malaria. Reference has already been made to **Acute Congestion** (p. 765) and to **Cloudy Swelling** (p. 190).

SUPPURATIVE HEPATITIS (**Abscess of the Liver**) occurs in various forms :—

(*a*) **Tropical abscess** (**amœbic abscess**)[1] is sometimes found without active symptoms of dysentery, though in some of these cases ulceration of the intestine is present. As a general rule, however, the presence of dysenteric ulceration is indicated by definite clinical manifestations, and the abscess is a secondary manifestation of the ulceration. The abscess in the liver is most frequently a solitary one, but two or more abscesses may be present, occurring perhaps in series, so that, on post-mortem examination, each may show a different stage in the process of development. The abscess usually takes origin deep in the substance of the liver, and may gradually make its way to the surface of the organ, there giving rise to the formation of sinuses which open through the diaphragm, through the abdominal wall, or into the colon. The contents of the abscess, thick, creamy, and of a pinkish colour, consist of fragments of broken-down liver-tissue, with or without pus-cells. There may be no sign of inflammation in the surrounding tissue, but, in chronic abscesses, the wall shows the definite formation of cicatricial fibrous tissue (Fig. 436). **On microscopical examination,** *Entamœba histolytica* may or may not be found in the contents of the abscess

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[1] *See also* under *Entamœba histolytica*, p. 363 : and Amœbic Dysentery, p. 748.

(Fig. 193, p. 363); but, in the necrosing liver-tissue forming its wall, they are present often in considerable numbers. The amœbæ may also be found in vessels at some distance from the local focus. Secondary infection with various bacilli, especially those of the colon-typhoid group, and micrococci, is not infrequent. The amœbæ pass to the liver from the intestine by way of the portal vein and its tributaries.

(*b*) **Pyæmic abscesses** (Fig. 437) are usually multiple and may be widely spread in the liver, or localised to definite areas. They are commonly secondary to a septic phlebitis of the portal vein—the source of the infection being usually in the large intestine and appendix, and frequently causing, in the first instance, a septic thrombosis of one of the mesenteric veins. A similar condition is due sometimes to direct thrombosis of the vein, and this may be produced by ulceration into it, or by the pressure upon it, of a gall-stone impacted in the bile-ducts, or by the severe inflammatory changes which may follow this cause, even where ulceration has not taken place. On the other hand, abscesses occur without thrombosis. Thus in cases of pyæmia the causal bacteria which are in the blood may become lodged in the liver and give rise to abscess-formation. **On microscopical examination,** the contents of the abscess are seen to consist of degenerated and necrotic liver-tissue mixed with leucocytes of various kinds. The causal bacteria may also be found.

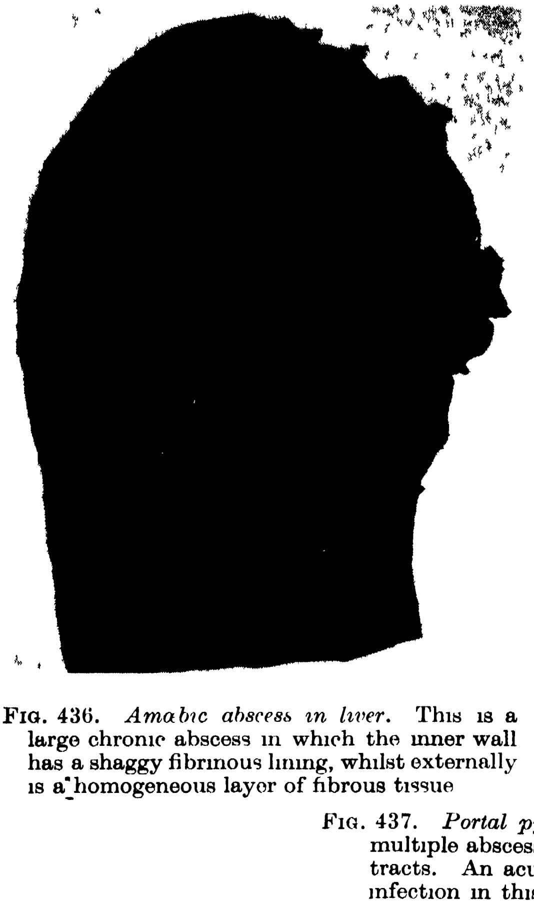

FIG. 436. *Amœbic abscess in liver.* This is a large chronic abscess in which the inner wall has a shaggy fibrinous lining, whilst externally is a homogeneous layer of fibrous tissue

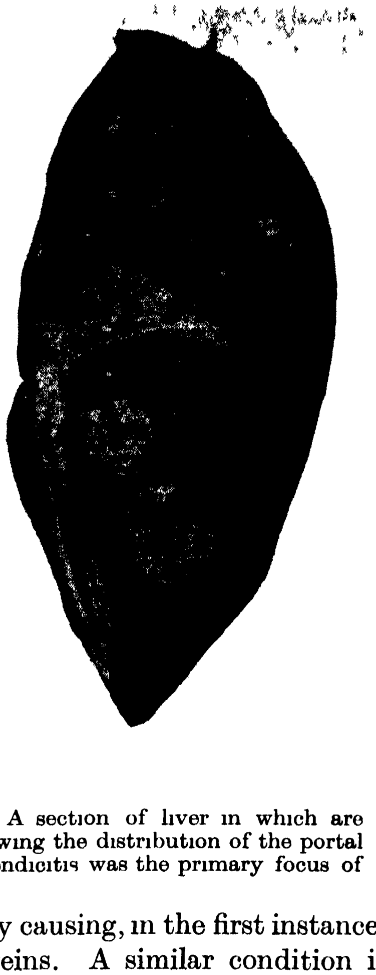

FIG. 437. *Portal pyœmia.* A section of liver in which are multiple abscesses following the distribution of the portal tracts. An acute appendicitis was the primary focus of infection in this case.

(*c*) **Biliary abscesses** or collections of pus in the biliary passages result from retained secretion in the passages becoming infected, the obstructing agents being gall-stones, cancer, parasites, etc. In other instances, there may be a diffuse suppurative condition of the bile-passages (**suppurative cholangitis**) with the formation of multiple abscesses (Fig. 438). The infecting organism is usually one of the members of the colon-typhoid group.

FIG. 438 *Suppurative cholangitis.* This section of liver is riddled with abscesses following a portal distribution and arising from bile-ducts

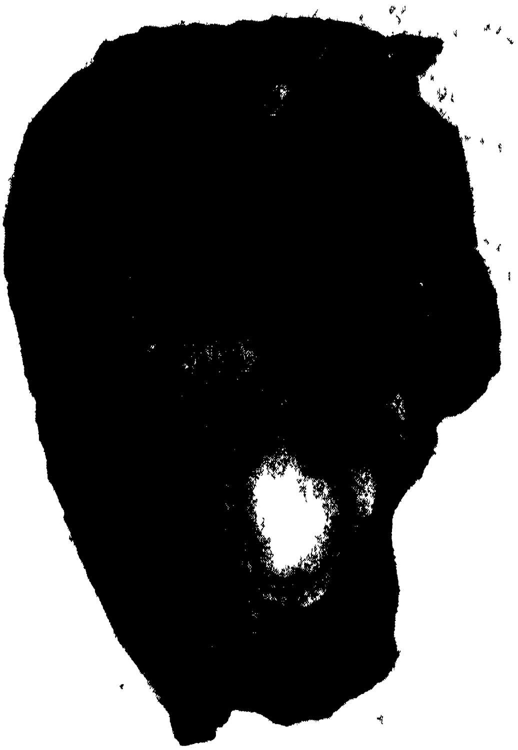

FIG. 439. *Syphilis of the liver.* Several large gummata, pale with well defined margins—are seen in the substance of the liver.

(*d*) **Abscesses of the liver** due to infection with *Streptothrix actinomyces*, or resulting from suppuration in hydatid-cysts and other causes may also occur, but present no important features which distinguish them from similar abscesses elsewhere.

Tuberculosis of the Liver :—(p. 76, Granulomata).

Leprosy :—(p. 79, Granulomata).

Syphilitic Disease of the Liver : (p. 85, Granulomata). (Fig. 439.)

Actinomycosis :—(p. 91, Granulomata).

TUMOURS :—

Angiomas occur, generally on the surface of the organ, as dark-red or purplish, slightly elevated areas, which are either encapsuled, or merge gradually into the surrounding liver-tissue. They vary in size, but are usually small and solitary. Occasionally they are multiple, and may be found even in large numbers, not only on the surface, but sometimes in the substance, of the liver. They occasionally occur as part of a " multiple-tumour syndrome," with the presence of angiomas or other tumours elsewhere, *e.g.*, in the brain, retina, etc. (*see* Lindau's disease, p. 1131, von Hippel's disease, p. 1132). **On microscopical examination,** the tumours are found to be of the cavernous type (p. 332 and Figs. 164–5, p. 333).

Adenomas are solitary or multiple, and appear as nodular masses, with a varying degree of encapsulation. They are sometimes associated with cirrhosis of the liver (p. 773), though they may occur independently of that condition. The cells forming the glandular structure of the tumour resemble those of the hepatic tissue proper, except that they are usually larger. Some authors hold that these so-called **adenomas** are not true glandular tumours, but merely portions of liver-tissue which have been isolated or newly-formed in the cirrhotic process. There seems little doubt that some of the primary malignant growths of the liver have their starting-point in such " adenomas " (*see* next page).

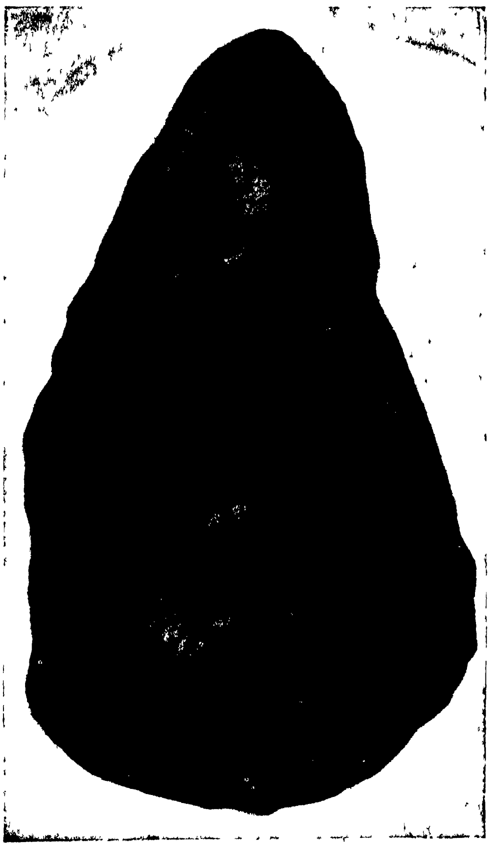

FIG. 440. *Primary malignant adenoma* of liver, liver-celled cancer, or " hepatoma."

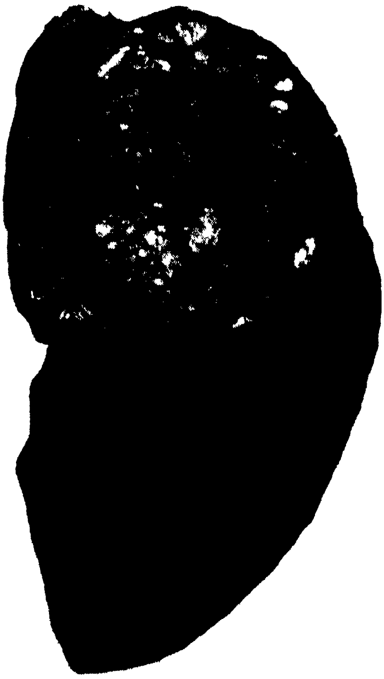

FIG. 441. *Primary liver-celled carcinoma.* A large nodule of tumour occupies the upper part of the liver—which is cirrhotic.

Primary sarcomas have been described, but are very rare; **secondary sarcomas,** especially of small round-celled type, are not **infrequent.**

Lymphomatous masses, resembling sarcomas, are seen in the interstitial connective tissue of the liver in some cases of leukæmia (pp. 630 and 634, and *cf.* Figs. 374 and 375). These consist of cells corresponding to the type of the leukæmia, but they are often more prominent in the lymphatic than in the myelogenous type. They occur more especially in the interstices of the portal tracts. In **Lymphadenoma** (p. 683), nodules, similar to those seen in spleen and lymph-nodes, occur, also especially in the portal tracts.

A few cases are on record of adrenal tissue being present in the liver, and tumours may arise from this.

Primary carcinoma develops occasionally in the liver, originating sometimes in connection with the bile-ducts, though more usually it arises directly from the hepatic cells themselves (liver-celled cancer or " malignant hepatoma ") (Figs. 440–1 and 2). Of the latter variety, most of the cases occur in connection with cirrhotic conditions of the liver—including the cirrhosis forming part of the hæmochromatosis-complex (pp. 227–8): and some at least of these carcinomas, as noted above, have their origin in the so-called simple adenomas. Those occurring without antecedent cirrhosis are often more

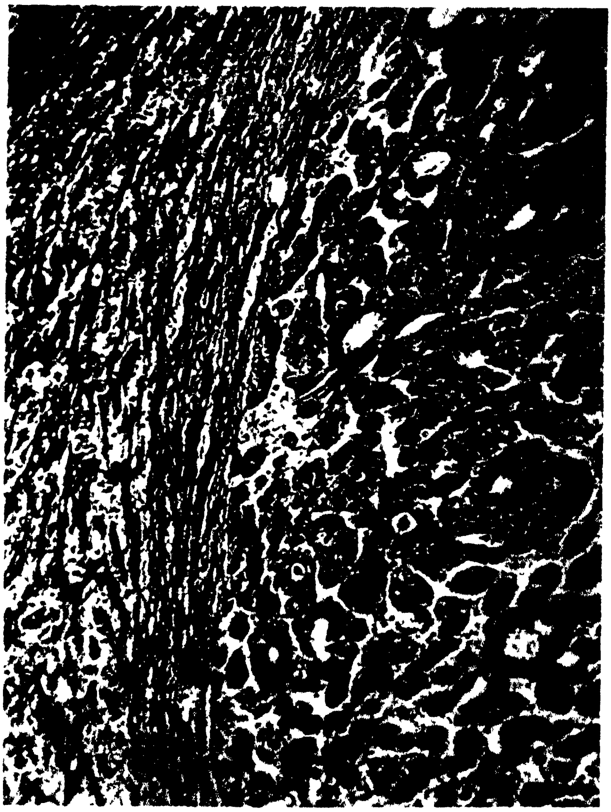

FIG. 442. *Primary Liver-celled Carcinoma* or *Malignant Hepatoma.* Showing irregular columns of large cells, resembling those of the liver, but with aberrations in size, appearance of the nucleus, etc. Hæmatoxylin and eosin. × 100.

atypical in cell-character and more malignant, giving rise to secondary deposits in the lungs and elsewhere. Those superadded to cirrhosis tend to invade the portal veins—and so increase the portal obstruction—but metastases elsewhere are infrequent.

In **tumours of the bile-duct variety**, the new-growth forms usually one or more nodular masses which are adenomatous in type, the glandular spaces being lined by cylindrical or more irregularly-shaped epithelium. These tumours generally remain localised, but occasionally give rise to secondary growths. Sometimes, the growths are very rapidly produced and extremely vascular. In the **liver-celled type,** the cells are arranged in masses or in thick irregular columns and often show great irregularity in size and shape, though still maintaining a general resemblance to the liver-cells from which they originate (Fig. 442); the surviving liver-tissue and in some cases the tumour-nodules may be deeply bile-stained.

Hæmangio-endotheliomas (p. 332) may be primary in the liver. They form hæmorrhagic masses throughout the organ and resemble secondary deposits of chorionepithelioma. They consist of numerous imperfectly formed vessels which invade and destroy the adjacent liver-cells.

Secondary carcinomas, spreading from the gall-bladder, may invade the liver; but most of the secondary growths attacking the liver extend to the organ by way of the portal circulation or by lymphatics from tumours in the stomach, intestine, bronchi, breast (Fig. 186, p. 348), etc. The secondary nodules may be very numerous. They are usually irregular in shape, pale in colour, and, if near the surface of the organ, show themselves as nodular elevations with very frequently a depressed centre (umbilication). On section, the centres of many of the nodules show yellowish areas of necrosis. Hæmorrhage into the tumour-tissue is of frequent occurrence. In the liver, secondary growths of malignant melanomas (whether these be regarded as "sarcomas" or as "melanocarcinomas") are usually numerous as part of their general dissemination throughout the body (Fig. 155, p. 322).

In microscopical characters, the secondary growths reproduce the characters of the primary tumours from which they originate—adeno-carcinomas of the stomach or intestine giving rise to adeno-carcinomas in the liver, a squamous epithelioma of the œsophagus forming a similar epithelioma in the liver, and so on. **Deciduoma malignum** or **chorionepithelioma** (pp. 352, 909–10, and 924–6) may give rise to secondary growths in the liver. It is not uncommon to find cancerous infiltration in those portal vessels by which the infective material has been conveyed. The nodules of this tumour are usually hæmorrhagic.

As a result of pressure upon the hepatic cells, upon the bile-ducts, or upon the portal vessels, atrophy, jaundice and ascites may occur in cases of widespread tumour-growth in the liver; though, in some cases, there may be very extensive destruction of liver-tissue without jaundice or ascites.

CYSTS IN THE LIVER :—

It is not common to find true cysts in the liver, though cystic disease of this viscus (Fig. 443, p. 784) is sometimes seen in association with cystic disease of the kidney. Such cysts are usually minute, but may reach from a quarter-of-an-inch to an inch in diameter. They always result from the dilatation of small bile-ducts. Large cystic spaces, due also to dilatation of the bile-passages, are sometimes seen throughout the liver. Congenital abnormality at the outlet, or obstruction due to some chronic inflammatory condition, with or without the presence of calculi, is the usual causal factor in these cases.

Small pseudocysts occasionally result from the softening and absorption of necrotic areas of liver-cells. The occurrence of "honeycombing" of the liver from the formation of gas by putrefactive organisms has already been mentioned pp. 236–7, and Fig. 111 : and p. 766), and cysts due to parasites, *e.g.*, hydatids, are described on p. 401 *et seq.*

FIG. 443. *Congenital cystic disease of liver.* There are throughout the liver many thin-walled cysts varying greatly in size.

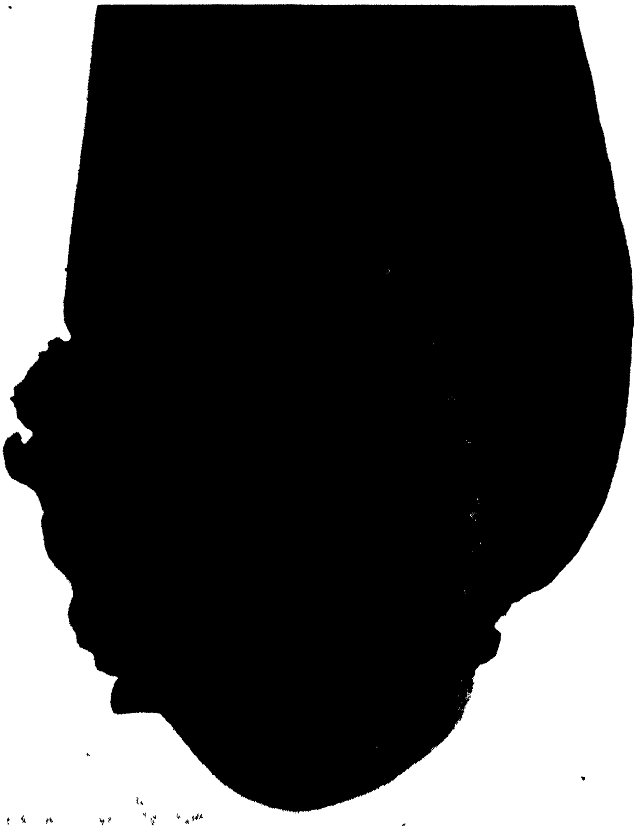

FIG. 444. *Hydatid-cyst in liver.* The ectocyst is thrown into folds and detached from the fibrous wall formed by the liver around it.

PARASITES OF THE LIVER :—

Hydatids of the liver (Fig. 444 above, and Figs. 221–2, pp. 401–2) are described under **Parasites** (p. 400). **Abscess-formation,** due to *Entamœba histolytica*, is referred to on pp. 363 and 778–9 (Fig. 436).

Fasciola hepatica and *Clonorchis sinensis* occur in the bile-ducts, and *Schistosoma hæmatobium* and *S. japonicum* in the portal vessels. A few human cases of coccidiosis of the liver—an infestation common in rabbits—are on record (p. 375, and Fig. 199, p. 376).

DISEASES OF THE GALL-BLADDER AND BILE-DUCTS

Anatomy and Physiology:—

The gall-bladder at its neck forms an acute angle with the cystic duct. This duct lies in the gastro-hepatic omentum and there joins the hepatic duct to form the common bile-duct. The terminal half-inch of the common bile-duct is embedded in the wall of the duodenum and ends in the **ampulla of Vater.** This ampulla extends into a papilla which generally projects into the lumen of the duodenum. At its opening into the latter, where the duct is narrowest, it is surrounded by a sphincter which regulates the flow of bile. Two lymph-nodes lie in the gastro-hepatic omentum by the side of the bile-duct, and, if calcified, may be mistaken for gall-stones. The common bile-duct in its second portion lies between the head of the pancreas and the duodenum. The intra-hepatic ducts are formed by the junction of bile-capillaries, and these connect with a fine intracellular network of channels which surround but do not enter the nucleus of the cell. The mucous membrane of the gall-bladder has a reticulated appearance, is lined by columnar epithelium, and secretes mucus. In the ampullary part of the bile-duct, there are submucous glands lying in crypts and folds, which are liable to infection and inflammation.

The function of the gall-bladder is to store and concentrate bile. Intermittently it contracts, forcing bile into the duodenum.

JAUNDICE. This is not a disease but merely a symptom, and the pathological lesions associated with it are of some importance, and have been mentioned already (pp. 228 and 769, *et passim*). The mechanism of bile-production and the general or localised pigmentation which results from its accumulation in the body-fluids and tissues are dealt with on p. 229.

CHOLANGITIS AND CHOLECYSTITIS. Inflammation of the bile-ducts and **inflammation of the gall-bladder** may arise independently of each other, or one may be secondary to the other. Moderate degrees of cholangitis are common—the inflammation in such cases being generally confined to a short portion of the bile-duct extending upwards for about half-an-inch to an inch from its opening into the duodenum. The condition is usually one of catarrh, and the swelling of the lining membrane of the duct causes partial or complete obstruction to the outflow of bile, with consequent jaundice. The infection may spread more widely, and may extend to the gall-bladder.

The **catarrhal form of cholangitis** may be the result of the direct spread of the inflammatory process from the duodenum; or it may occur as a result of the irritation of gall-stones; and is found sometimes in the smaller ducts during specific fevers, *e.g.*, typhoid, pneumonia, etc., although, as already noted, there is often liver-cell damage as well in such cases. In certain cases, **suppuration** takes place, the purulent exudate extending widely and involving the gall-bladder, which may become distended with pus—**empyema of the gall-bladder.** In some patients with **suppurative cholangitis,** there has been a pre-existing obstruction, with dilatation of the passages and accumulation of biliary products—these products becoming infected by bacteria derived directly from the intestine or reaching the passages by way of the blood. *Bact. coli,* streptococci and staphylococci, typhoid and paratyphoid bacilli, are among the commonest organisms found in such conditions.

During an attack of typhoid or paratyphoid fever, the gall-bladder frequently becomes infected with the specific organisms of these diseases—the cholecystitis set up being either catarrhal or suppurative. According to Scheller,[1] the bacilli are found in the form of capillary emboli in the mucous membrane. The bacilli retain their vitality and virulence in the gall-bladder for a very considerable time after recovery from the acute attack, and it is probable that some of the " recurrent " cases of typhoid and paratyphoid fever are thus to be explained. More important, however, is the fact that the fæces of such patients contain the bacilli, often only intermittently, and that for years after an attack these " carriers " are potential propagators of the disease. The source of some serious outbreaks of typhoid fever, especially in asylums, workhouses, and similar institutions, has been traced to these carriers.

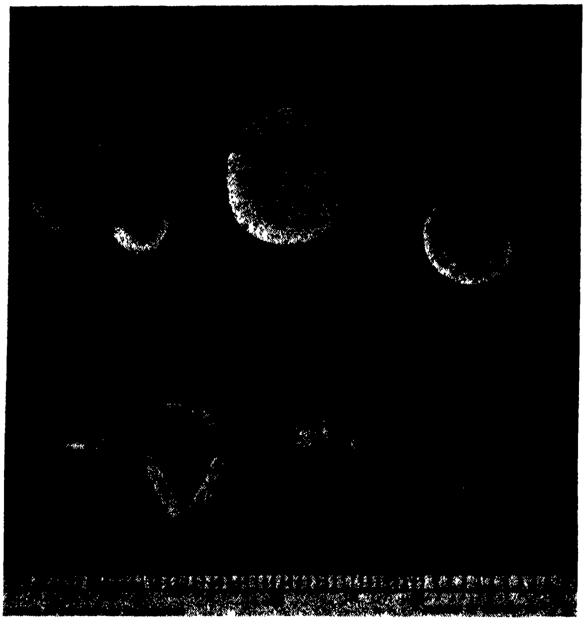

FIG. 445. *Biliary calculi.* In the upper row are examples composed mainly of cholesterol. In the lower row are faceted calculi showing a considerable admixture of bile-pigment with cholesterol.

The gall-bladder in the acute forms of cholecystitis is distended with bile-stained mucus, or with pus ; its mucosa is congested and the inflammatory process may spread through its coats to the peritoneum, giving a local peritonitis. Perforation may occur. In the more chronic forms, the result usually of repeated minor attacks of infection and often associated with gall-stones, the gall-bladder may have its walls much thickened, with adhesions to surrounding structures, and its mucosa reddened and ulcerated in some parts, whilst in others there may be hyperplasia of the mucosa.

GALL-STONES (BILIARY CALCULI: CHOLELITHIASIS). These are of frequent occurrence, especially in people past middle life, and in those of sedentary habits, but they occur at any age. They are commoner in the female than in the male, but not more common in married than in single women. At **post-mortem**, gall-stones are frequently found without any previous clinical indication of their presence.

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[1] R. Scheller, *Zentrabl. f. Bakt. u. Parasit.*, 1908, Beilage zu Abt. i, **42**, 50. Referate.

They are composed of cholesterol, bile-pigment, mucus, and salts of calcium and magnesium, the composition varying in different forms (Fig. 445). They may be single or multiple, and when multiple they are commonly faceted. The **single,** or solitary, gall-stone is often large, usually ovoid, and frequently composed almost entirely of cholesterol. It is whitish in colour, of wax-like consistence, and on section may show a crystalline structure of cholesterol masses, sometimes in laminæ, often with a small central core of pigmented debris. Single stones, composed of laminæ of cholesterol mixed with bile-pigment, also occur. **Multiple** calculi are commoner, varying from a few to hundreds in number. They are faceted and vary in colour from yellow to almost black, and are composed of variable amounts of cholesterol, bile-pigments, calcium and magnesium salts, and mucus. Small, soft, dark masses composed mainly of bile-pigment, are frequent—biliary sand or gravel—and may be a stage in the formation of larger stones.

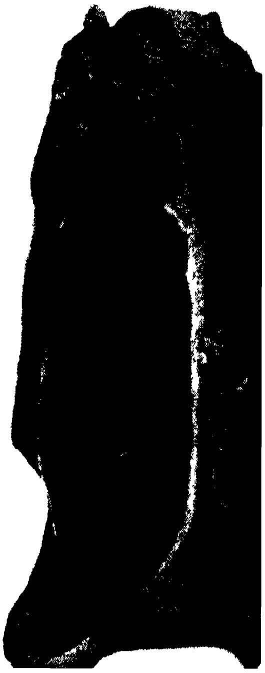

FIG. 446. A gall-bladder packed with faceted calculi composed of mixed bilirubin and cholesterol.

FIG. 447. *Cholesterosis, or "strawberry gall-bladder."* The outer wall of the gall-bladder is fibrosed and thickened; the mucosa is studded with minute projections—light in colour from deposit in them of cholesterol.

Cholesterosis ("strawberry gall-bladder" (Fig. 447). This is a condition of obscure ætiology, sometimes found unexpectedly *post mortem*, sometimes at operation following symptoms of mild cholecystitis. It is not infrequently associated with biliary calculi. The mucosa of the gall-bladder is studded with a number of yellowish spots, due to deposits of cholesterol within macrophages under the epithelium.

The mode of **formation of gall-stones** has given rise to considerable controversy. By some authorities, **infection** is claimed to be the starting-point, causing a nucleus of mucus or cell-debris on and in which the bile-salts and cholesterol precipitate. Bacteria have been recovered from calculi and from bile, but in many cases these are sterile. By others, the essential factor is said to be some **metabolic disturbance** leading to precipitation of cholesterol, and subsequent infection. **Hypercholesterolæmia** (*cf.* p. 202) is often present in cholelithiasis, but only, apparently, in cases where jaundice has occurred. Its presence in pregnancy was assumed to be a factor predisposing to the formation of gall-stones, but statistical studies have not supported this contention.

Concentration of bile may also be a factor leading to the precipitation of cholesterol. An appropriate concentration of bile-salts is required to keep cholesterol in solution, and observations [1] suggest that there is a reduction of bile-salts in the bile where calculi are present; also that liver-damage may reduce the bile-salt output. Infection of the gall-bladder may also alter the ratio of bile-salt and cholesterol. Thus both factors, metabolic disturbance as represented by liver-damage, and infection, may determine the occurrence of gall-stones.

Effects of Biliary Calculi. These may be mechanical alone, or may be complicated by infection. The gall-bladder becomes inflamed, ulcerated and even perforated. Perforation has occurred into the colon, or into the peritoneal cavity, or even posteriorly, causing infection around, and thrombosis in, the portal vein. Adhesions often form around the inflamed organ.

The stone may lodge in the neck of the gall-bladder and produce dilatation. If infection is present in the lumen, pus may fill the organ—**empyema of the gall-bladder**—with extension to its outer surface or even actual rupture. If not infected, the gall-bladder may remain distended, the bile is absorbed and ultimately only clear mucus may be left. Sometimes the gall-bladder becomes contracted and fibrosed around the stone or stones. There may even be calcification in its wall. If the stone passes down into the common duct, it is likely to lodge in the ampulla (duodenal papilla) and produce an obstructive jaundice. It may ultimately be passed into the duodenum, either through the ampulla itself, or by an opening increased by ulceration. Occasionally, a stone lodges in the common duct and produces intermittent obstruction with recurring jaundice. Long-continued obstruction of the common duct may give rise to biliary cirrhosis. Cases are on record of a large gall-stone, having escaped by ulceration into the intestine, causing intestinal obstruction.

In old-standing cases of gall-stones, malignant disease (p. 790) sometimes supervenes in the gall-bladder.

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[1] Newman, *Beitr. z. path. Anat.*, 1931, **86**, 187; Andrews and others, *Arch. of Surg.*, 1932, **25**, 796, 1081.

Obstruction of the bile-ducts may also be caused by hydatid-cysts, liver-flukes, etc., pressure on the ducts from outside by tumours, aneurysms of

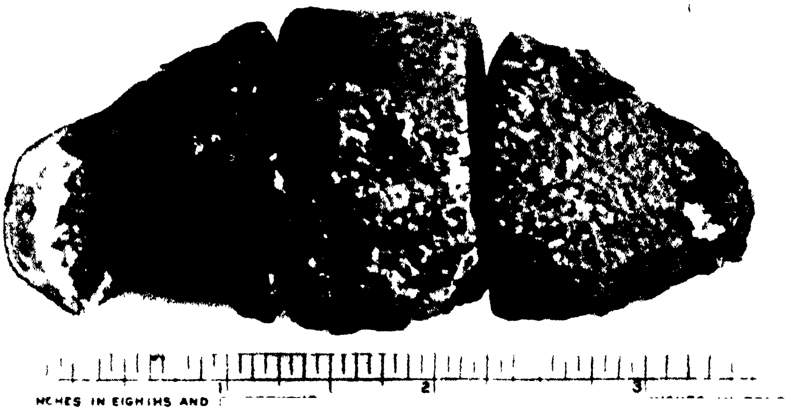

FIG. 448. *Large Gall-stones.* From case of an elderly female, in which they ulcerated through into the transverse colon, and were passed *per rectum*—the patient recovering. (W. E. C. D.'s case, *Lancet*, 1906, ii, 221.)

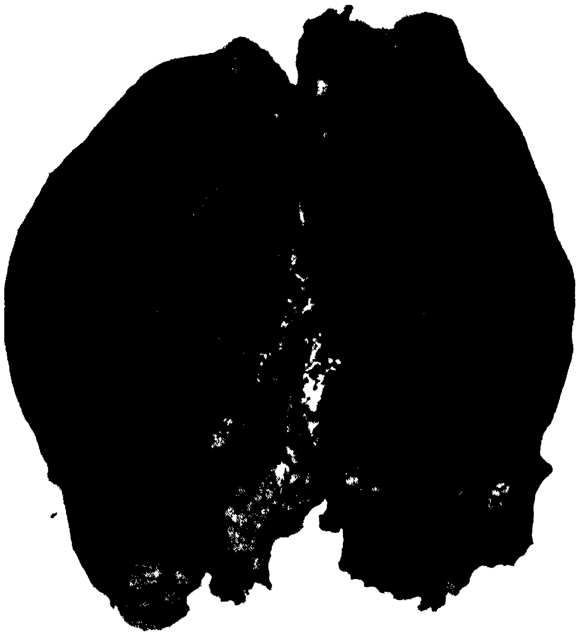

FIG. 449. *Primary carcinoma of gall-bladder.* A large gall-stone lies within the gall-bladder, the wall of which is thickened from fibrosis and carcinomatous change. The adjacent areas of liver are extensively infiltrated by tumour and the liver-structure obliterated.

the hepatic artery, enlarged lymph-nodes, etc., or by stricture of the duct itself by inflammatory changes or the presence of malignant disease. Congenital obliteration from non-development of the ducts also occurs. The results of all these are jaundice, and, in some cases, biliary cirrhosis.

TUMOURS. The most usual primary tumours of bile-ducts or of gall-bladder are **carcinomas,** commonly of adenomatous type. In the gall-bladder, especially if the site of old-standing gall-stones (p. 788), metaplastic squamous carcinoma sometimes occurs (Fig. 449). Small, slow-growing tumours of low-grade malignancy, mostly adenocarcinomas, growing from the region of the opening of the common bile-duct into the duodenum, or from the " ampulla " if present, have been described by Gordon-Taylor [1] and others.

Metastases from these, or from malignant tumours of the liver or elsewhere, may invade or obstruct the bile-ducts.

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[1] " The Radical Surgery of Cancer of the Lower End of the Common Bile Duct and Adjacent Pancreas " (Hunterian Lecture), by G. Gordon-Taylor, *Brit. Med. Jour.*, 1942, *ii*, 119.

(From p. 762)

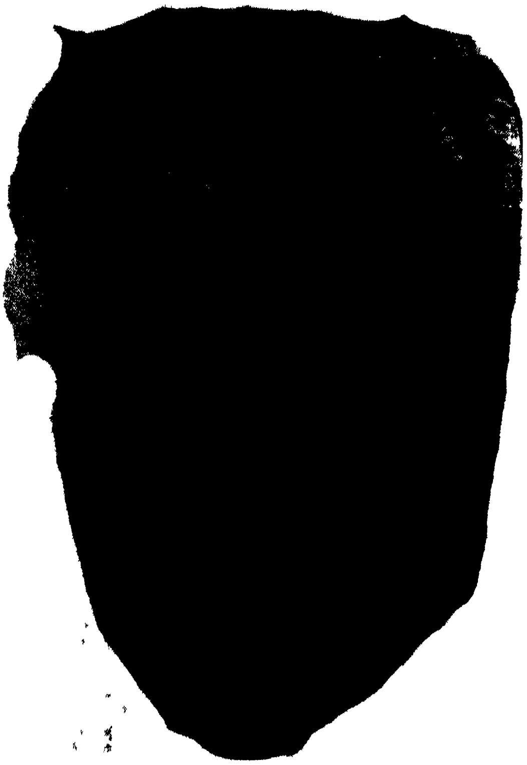

FIG. 421A. *Liver*, with a portion of diaphragm left in position to show how a folding of the diaphragm can produce a corresponding groove on the surface of the liver (*see* p. 762 and *cf.* Fig. 421, p. 763).

CHAPTER XXIII

DISEASES OF THE PANCREAS

Introductory:—

In its general structure, the pancreas resembles a salivary gland, being made up of a number of glandular acini loosely held together by fibrous connective tissue. The ducts of these acini communicate with the main pancreatic duct (duct of Wirsung), which opens —usually along with the common bile-duct—into the duodenum. An accessory duct (the duct of Santorini) is present in a more or less developed condition in 50 per cent. of people. This duct may open directly into the duodenum at a point nearer to the pylorus than the duodenal papilla (ampulla) and thus form a second channel by which the pancreatic secretion may enter the duodenum. Scattered throughout the substance of the organ, there are rounded or irregular masses of cells, arranged in cell-columns and separated from the gland-acini. The epithelial cells within these islands (the islands of Langerhans) lie in contact with the endothelial cells of large capillary blood-vessels, and it is generally accepted that the secretion from these islands passes directly into the blood. Into the controversy of the development of the islets and their relation to the glandular acini it is not necessary to enter here. The glandular tissue produces the various enzymes concerned with the digestion of fats and proteins. The islets are associated with insulin-production and thus with carbohydrate-metabolism.

Fig. 450. *Accessory Pancreas.* The nodule projecting from the surface consists of pancreatic tissue; it has been incised to show its solid lobular character. It was situated in the wall of the jejunum eight inches distal to the duodenum.

By means of special staining methods devised by Bensley and others, the cells of the islets have been shown to contain two different types of granules—" A " and " B " (or α and β). Of these the " B " type appears to be closely related to, if not identical with, insulin. Unfortunately, these granules are very susceptible to autolytic changes and disappear so quickly after death that in human post-mortem material it is impossible to identify them. But in the experimental animal, where a large part of the pancreas has been removed and excess sugar given, exhaustion of, or degenerative changes in, the " B " granules are associated with diabetes, *i.e.*, lack of sufficient insulin. " B " granules have also been demonstrated in human biopsy-material from islet-adenomas associated with hypoglycæmia from excess of insulin.

CONGENITAL ABNORMALITIES. The presence of small accessory pancreatic glands in the omentum, mesentery and elsewhere is by no means uncommon. They may occur also in the gastric or intestinal walls, where they are sources of weakness and where they may—especially in the case of the intestine—lead to the production of diverticula, at the distal ends of which the small accessory glands may be found on section (Alexis Thomson). The commonest site for these pancreatic " rests " or ectopic fragments of gland-tissue is in the wall of the jejunum (Fig, 450, p. 791) though occasionally they occur in the duodenum and in the stomach. Such " rests " are usually provided with a duct leading to the lumen of the bowel. In rare instances, tumour-growth (pp. 798–9) may arise from these supernumerary glands. **Annular pancreas** is a rare anomaly in which the gland encircles the duodenum and may even cause obstruction of it. For " Congenital Cystic Disease of the Pancreas," *see* p. 799.

POST-MORTEM SOFTENING, due chiefly to auto-digestion, is frequent, occurs early, and the whole pancreas may become involved. Microscopically, the nuclei of the gland-cells in the affected areas do not stain and the cells undergo shrinkage, so that the connective tissue becomes more evident.

TOTAL EXTIRPATION of the organ is followed by wasting, glycosuria, and polyuria, *i.e.*, all the essential symptoms of diabetes mellitus (p. 800) ; and these symptoms arise also in certain cases of disease, especially if accompanied by fibrosis of the organ.

WOUNDS OF THE PANCREAS allow the escape of pancreatic secretion, and this gives rise to necrotic changes in the fat of the omentum, etc. (p. 247). Cases have been described in which the pancreatic secretion has collected in the lesser sac of the peritoneum and given rise to a pseudo-cyst.

HÆMORRHAGE INTO THE PANCREAS may be found as minute petechiæ, or in the form of large hæmorrhagic infiltrations. The former occur in purpura, scurvy, and in septicæmic and toxic diseases in general. The latter, however, are more important and are generally described under the term " **hæmorrhagic pancreatitis** " (*see later*, p. 794).

Hæmorrhagic infiltration results from the destructive changes produced by tumours, especially sarcomas and carcinomas ; and it may be present, though usually only in minor degree, as a sequel of chronic venous congestion in cardiac disease, pulmonary disease, or cirrhosis of the liver. Further, scurvy, purpura, the infective fevers, and phosphorus-poisoning, though giving rise usually to minute hæmorrhages, may also be the cause of larger extravasations ; and hæmorrhages from embolism, or resulting from fat-necrosis, are found. Injury of the pancreas may also be a cause of hæmorrhage.

OBSTRUCTION OF THE PANCREATIC DUCTS. Tumours of the head of the pancreas, **gall-stones** in the common bile-duct, **aneurysms** in neighbouring vessels, and **pancreatic calculi** in the duct itself (Fig. 451), may cause occlusion ; and the portion of the gland which is drained by this occluded duct may, if the obstruction is prolonged, become hard and shrunken. On **microscopical examination,** such areas show the pancreatic cells largely destroyed and replaced by scar-tissue, the acini having disappeared, or having become dilated and lined by flattened epithelial cells. Even in advanced cases, the islet-tissue may survive.

Similar appearances are seen after experimental ligature of the pancreatic duct; but, if the accessory duct is patent, the portion of the pancreas drained by it may remain healthy. The islands of Langerhans remain uninjured and, in advanced cases, may be the only intact original glandular tissue left.

The chronic interstitial pancreatitis produced in this way by ligature or obstruction of the duct may not give rise to glycosuria, even though the interstitial changes are considerable.

Absence or inadequacy of the pancreatic secretion interferes with the normal digestion of fatty substances and proteins in the intestine; and, in such cases, the stools contain excess of undigested, *i.e.*, unsplit, neutral fat, and protein such as muscle-fibre.

Results. In severe hæmorrhage, death may supervene from shock or from pressure on the cœliac axis. If death is not thus suddenly caused, extensive fat-necrosis (p. 247) results, not only in the pancreas but also in the surrounding fat, especially of the omentum and mesentery, as well as in the adipose tissue in other parts of the body. In certain cases in which the primary hæmorrhagic condition has not proved fatal, a chronic inflammatory change with overgrowth of fibrous tissue follows.

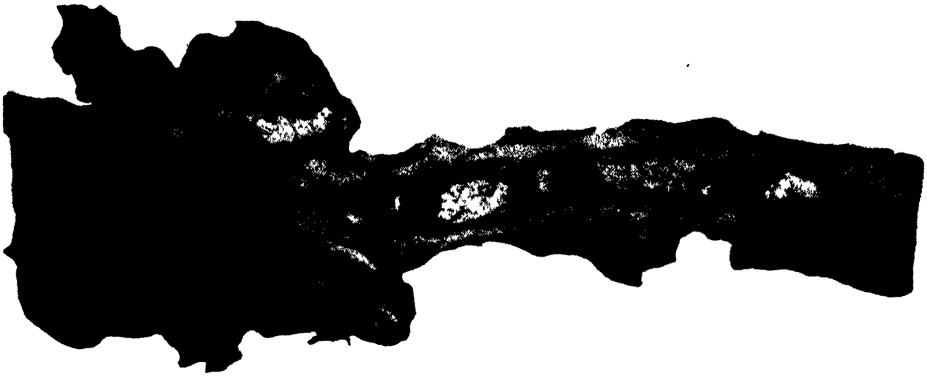

FIG. 451. *Pancreatic calculi and atrophy.* Calculi of various sizes lie in the much dilated pancreatic duct. The pancreatic tissue is fibrous and greatly reduced in amount.

DEGENERATIVE CHANGES. Amyloid degeneration in the vessels of the pancreas is rare and when present is only part of a general amyloid change. **Fatty degeneration** may occur in the acinar cells. **Fatty infiltration** or **replacement** supervenes in the supporting tissue as a result of atrophy of the acinar tissue and in general adiposity. **Hydropic** and **hyaline** degenerations are frequent in the islets and are present in about 70 to 80 per cent. of cases of diabetes. **Pigmentation** may occur in or around the seat of hæmorrhages, but is especially prominent in cases of " bronzed diabetes " of hæmochromatosis (pp. 227, 774, 804 and 1070), in which it is associated with pigmentation in other organs and in the skin, together with changes in the central nervous system (p. 1070). The pigment is partly in the form of an iron-free compound, but is largely hæmosiderin, and may be found in enormous quantity and give rise to cirrhosis of the pancreas.[1]

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[1] J. M. Beattie, " Hæmochromatosis, with Diabetes Mellitus," *Jour. Path. and Bact.*, 1904, **9**, 117.

Atrophy of the pancreas occurs in old age and in wasting diseases ; and in these cases is usually general throughout the gland. Localised atrophy may result from pressure or from obstruction of the ducts. In some cases of diabetes mellitus, the pancreas is atrophied ; and in carcinoma and in cirrhosis of the gland there may be a pronounced degree of atrophy of the secreting tissue. In cases of interstitial pancreatitis, the atrophy of the organ may be extreme.

Areas of **necrosis,** varying in size, are produced in the pancreas as a result of hæmorrhage or of inflammation ; and from the setting free of its fat-splitting ferment a special form of this condition occurs, particularly in the fatty tissue of the pancreas and the omentum, and in severe cases in the extra-peritoneal and even in the subcutaneous fatty tissue. This **fat-necrosis** appears in the form of minute greyish-white or yellowish-white opaque foci, or larger patches formed by the coalescence of these, and is usually associated with acute or chronic pancreatitis, tumour-formation, obstruction of, or injury to, the ducts. These foci should not be mistaken for tuberculous nodules or metastases of neoplasm, both of which project from the surface of the fat in contra-distinction to the necrotic fatty foci which are level with the surface. Small patches, analogous to those of fat-necrosis, but due to post-mortem autolysis of the gland and after-death digestion of fat by the liberated fat-splitting ferment, steapsin, are sometimes seen, but these have no associated congestion or hæmorrhage such as is seen in ante-mortem necrosis. **Microscopically,** the areas of necrosis are more or less homogeneous in appearance, and do not stain with osmic acid—the fat having become disintegrated, and probably converted into a compound of a fatty acid united with a calcium base. The pathology of this condition is described on p. 247.

INFLAMMATORY PROCESSES IN THE PANCREAS. These may be acute or chronic, and general or local. The epithelial elements are usually more or less damaged and, in the more chronic forms, the interstitial overgrowth is often considerable. Interference with function results ; in the acute forms the septic features, or the shock, usually overshadow any specific functional aspect, but, in the chronic forms, loss of tissue leads to incomplete digestion of fat and protein, and, in some cases, sugar-metabolism is also affected.

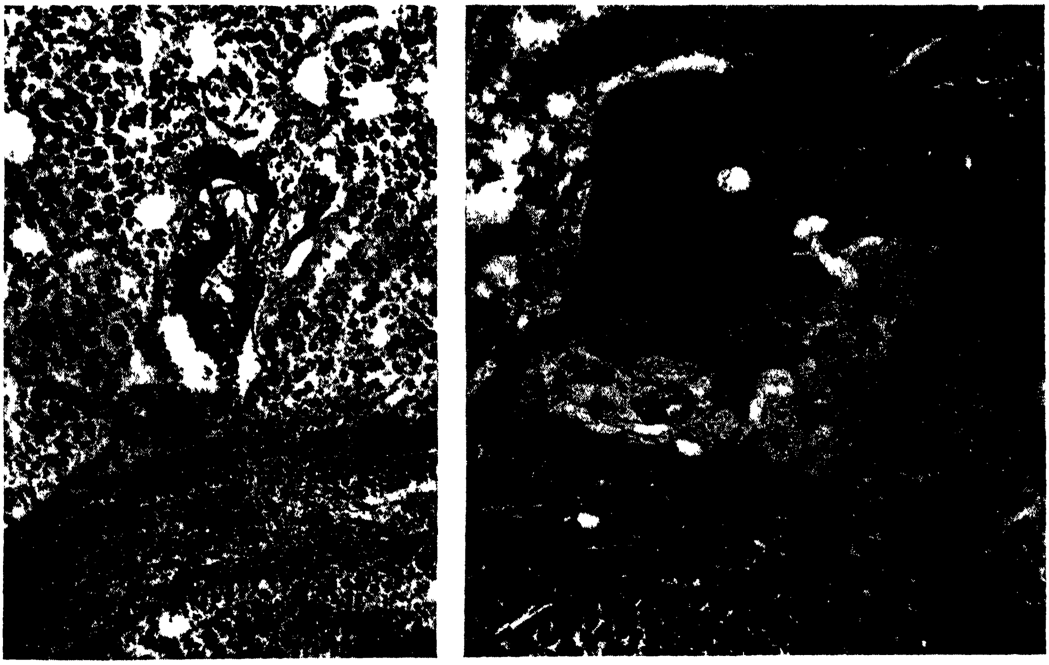
Various forms of pancreatitis are described :—

1. **Acute Hæmorrhagic Pancreatitis.** (Fig. 452). This is one form of " acute abdomen " as, clinically, it occurs suddenly with severe epigastric pain, vomiting and collapse.

While its origin may be infective, the effects are due mainly to the activating of the pancreatic enzymes *in situ*, with the result that extensive hæmorrhage (from proteolytic enzyme action) and fat-necrosis (*see above*) occur. Scattered patches or large areas of the pancreas become hæmorrhagic and necrotic and similar areas occur in the adjacent fatty tissue and over the peritoneum. We have seen small areas of fat-necrosis even in the fat of the anterior mediastinum and breast. There is a blood-stained exudate, serous or sero-fibrinous, in the peritoneal cavity. **Microscopically** (Fig. 453 A and B), the affected areas in the pancreas, and in the fatty tissue, show complete necrosis, with loss of structure of the cells and tissues, mingled with hæmorrhage and a variable amount of fibrinous exudate, usually with few leucocytes. The condition is frequently fatal, death occurring from collapse. If recovery occurs, the necrotic areas are

FIG. 452 *Acute hæmorrhagic pancreatitis* The pancreas (lying in the concavity of the duodenum) has been divided longitudinally to show the extensive hæmorrhagic infiltration (dark), especially of the body In the head, towards the tail and to a less extent in the body, are light patches of fat-necrosis

FIG. 453. *Acute hæmorrhagic pancreatitis*



(A)

A small blood vessel, the wall of which is necrosed and disintegrated, with hæmorrhage around and below it.

(B)

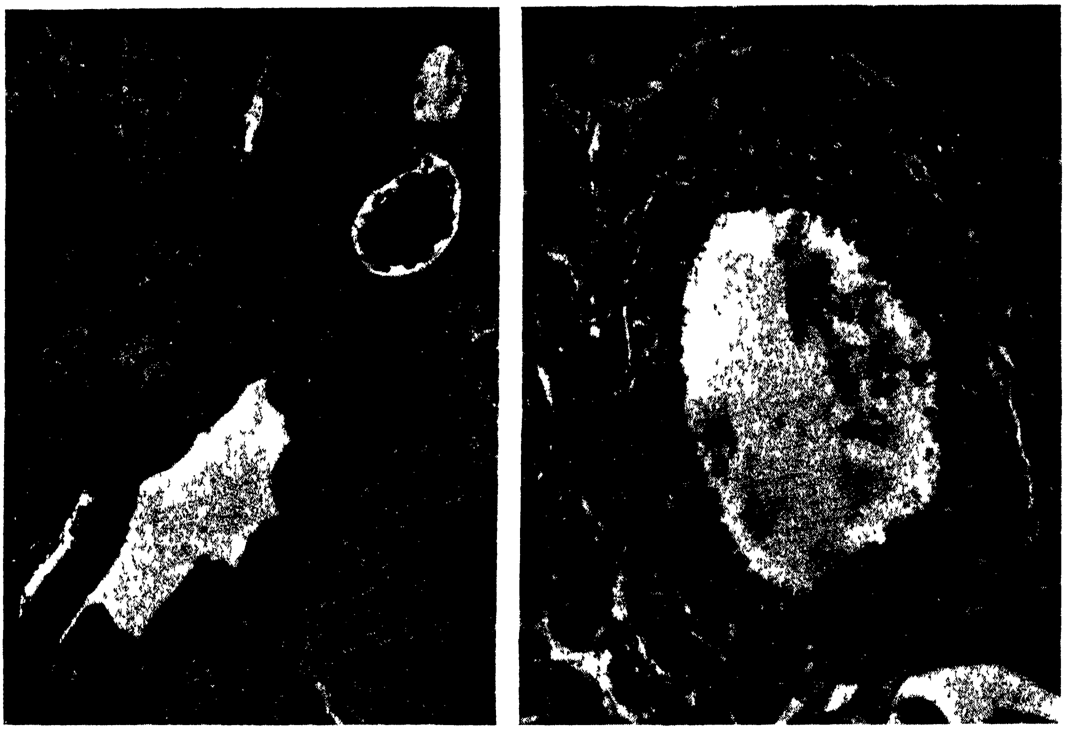
An area of fat necrosis (lower centre) with hæmorrhage below and to the right, and partially autolysed pancreas above it

Hæmatoxylin and Eosin. × 70

absorbed and replaced by fibrous tissue varying in degree, but in such cases enough pancreas has survived to carry out its functions.

Ætiology. The cause of the activation of the pancreatic enzymes *in situ* is often unknown, but it is frequently associated with obstruction of the orifice of the duct, or rather of Vater's ampulla, by gall-stones; and Opie (1910) suggested that bile reaches the pancreas by the duct of Wirsung, causing necrosis of, and hæmorrhage into, the cellular tissue. There is no doubt that the pancreatic tissue is very susceptible to the action of irritating substances. It has been shown experimentally that injection of substances such as sulphuric or nitric acid, bile, artificial gastric juice, and suspensions of various organisms, into the gland-substance, directly or through the ducts, gives rise to necrotic, hæmorrhagic, and suppurative conditions. Rich and Duff,[1] in an extensive study of this condition, have found that the pancreatic juice varies considerably in its tryptic content. The enzyme may be increased by feeding. The necrotic changes are produced by the trypsin, which destroys vessel-walls and so produces hæmorrhage. These authors found metaplasia of the epithelium

FIG. 454. *Metaplasia in pancreatic ducts.* (From same case as preceding figures.)



(A) × 85

The larger duct towards the lower left corner shows proliferation of its epithelium at one side. The smaller duct above and to the right has more uniform proliferation of its epithelium and is plugged with inspissated secretion.

(B) × 420.

High-power view of the small duct shown in the extreme upper right corner of A. There is considerable proliferation of its epithelium, the cells of which exhibit metaplasia from columnar to stratified polygonal type.

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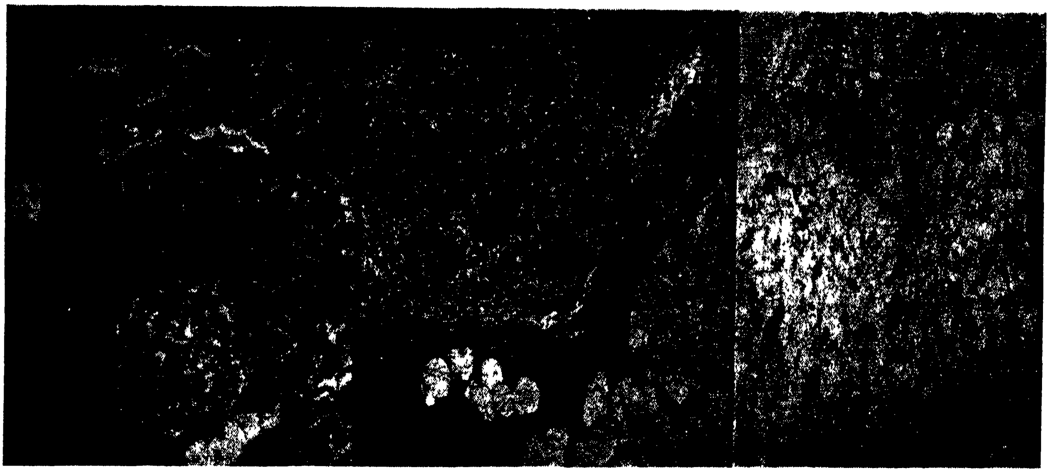
[1] *Bull. Johns Hopkins Hosp.*, 1936, **58**, 212.

of the ducts in many cases of hæmorrhagic pancreatitis, and consider that this is one cause of obstruction in the smaller ducts. The accumulation of pancreatic secretion containing its enzymes leads to distension of the ducts and their rupture, and the escape of the enzymes which then act on the tissues. The **ætiology** of the **chronic changes** is often obscure. Occasionally, an acute pancreatitis may pass on to the chronic interstitial stage (Fig. 455, A, B, C), but usually there is no antecedent acute history of this. Obstruction of the duct by pressure from without, or by foreign bodies, catarrhal processes, tumours or calculi from within, may give rise to interstitial changes in the organ. Thus, it sometimes arises as a result of gall-stones blocking the common outlet, pancreatic calculi, tumours, or catarrh of the duodenum. Toxic products of known or unknown nature must be regarded as important causal factors, and cases have been recorded which seem to have arisen secondarily to alcoholism, syphilis, purulent peritonitis, typhoid fever, influenza, mumps, etc. Such infective or toxic agents act possibly by producing gastro-duodenal catarrh which spreads up the pancreatic duct. It has been shown experimentally, by the injection of oil-of-turpentine, alcohol, agar, and other foreign substances into the pancreatic duct, that sclerosis of the gland may be produced. In some instances, the cirrhosis of the pancreas is associated with cirrhosis of the liver.

FIG. 455. *Healed pancreatitis.* Three representative areas in the same organ from a case of acute pancreatitis which recovered, but died some weeks later from an intercurrent infection.



(A) × 75. A portion of comparatively normal pancreas.

(B) × 65. Interstitial fibrous overgrowth around surviving acini.

(C) × 75. From tail-region, distal to B. Complete disappearance of all pancreatic tissue. only the supporting connective-tissue framework, containing fat, remaining.

2. **Acute Suppurative, Gangrenous, or Necrotic Pancreatitis**—though it may result as an extension of septic processes in the neighbourhood, as, for example, from a gastric or duodenal ulcer—is sometimes primary, the infection coming apparently from the intestinal tract by way of the ducts. The pancreas

in any of these conditions is swollen and extremely soft, and shows a varying number of necrotic foci or gangrenous cavities. Scattered abscesses may occur in the pancreas as part of the general infection in **pyæmia**.

3. **Chronic Interstitial Pancreatitis.** Various anatomical forms of this are recognised, depending on the distribution of the interstitial fibrosis which is the feature of the condition. Thus, it may be :—

(*a*) **Inter-lobular.** In this the inflammatory process is localised to the periphery of the lobules; and the cellular structure, with the islets of Langerhans, is affected only in the later stages.

(*b*) **Inter-acinar** or **Intra-lobular.** The new fibrous tissue is diffusely distributed and invades the lobules, separating the individual acini and invading the islets of Langerhans.

Cirrhosis of the pancreas is a combination of inter-lobular and inter-acinar changes, with great overgrowth of fibrous tissue.

In all the forms of interstitial pancreatitis, the organ in the early stages is hard and enlarged. The amount of interstitial tissue is greatly increased. In the later stages, there is atrophy, and, on section, very little of the glandular elements can be detected. **Microscopically,** the cells are atrophied or degenerated, and there is overgrowth of fibrous tissue, which may be cellular, but, more commonly, is dense, fully-formed tissue. In some cases, the interstitial overgrowth may be so great that almost the whole of the secreting-cells are destroyed. This interstitial pancreatitis may or may not be associated with glycosuria, and evidence of defective enzyme-function is seen in the form of digestive disturbances—unsplit fat and unaltered protein, *e.g.*, muscle-fibre, in the fæces.

Localised areas of interstitial pancreatitis occur. Thus, Lancereaux [1] described a case in which the middle third of the pancreas was merely a fibrous cord, and the left lateral third much atrophied. This condition was associated with diabetes mellitus.

Tuberculosis of the pancreas is rare (*cf.* p. 76). Miliary or solitary nodules are sometimes seen, and the organ may be involved from neighbouring tuberculous lymph-nodes.

Syphilis may give rise, as has been stated, to interstitial pancreatitis, and involvement of the pancreas is commonest in the congenital form of the disease. It is frequently associated with interstitial overgrowth in other organs, as, for example, in the liver and in the lungs.

TUMOURS AND CYSTS :—

Sarcoma may occur both as a primary and as a secondary growth, but it is rare.

Primary carcinoma, which may be an **adeno-carcinoma,** or a **spheroidal-celled cancer,** often of scirrhous, encephaloid, or occasionally of colloid, type, occurs in the pancreas, usually the head, with comparative frequency. It is often difficult at the stage reached in the post-mortem specimen to say exactly where the starting-point of such a tumour has been. While some of these have undoubtedly started from acinar tissue of the pancreas, others may have arisen from the bile-duct ampulla or other epithelial tissue in the neighbourhood.

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[1] Lancereaux, *Bull. Acad. de Méd.*, Paris, 1877, series 2, **6**, 588.

Primary tumours of islet-tissue are now recognised (Fig. 456). They are usually of benign-adenoma type, but adeno-carcinoma can also occur. The first tumour of this nature was recorded by Wilder in 1927.[1] The patient was a medical man who suffered from increasing hypoglycæmia (owing to excess of insulin produced by the tumour) and who eventually died with an islet-cell tumour in the tail of the pancreas with metastases in the liver. Since then a number of such cases have been recorded and in some the tumour has been successfully removed surgically, with disappearance of the hypoglycæmia. As already mentioned (p. 791), such tumours examined immediately after removal have shown " B " granules, and extracts of them have produced hypoglycæmia in animals. Hypoglycæmia may also occasionally be associated with hyperplasia of the islet-tissue in which no actual tumour-formation has been demonstrated (in this connection *see also* p. 804 and Fig. 459, p. 803).

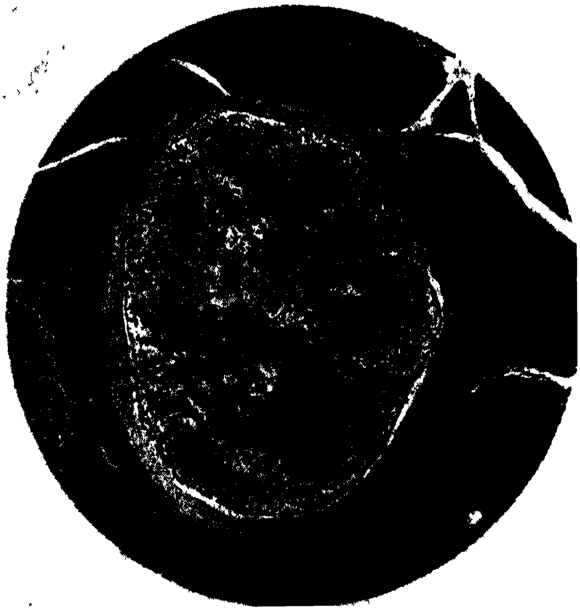

FIG. 456. *Adenoma of islet-tissue of pancreas.* The tumour is sharply circumscribed by fibrous tissue which demarcates it from the adjacent pancreatic parenchyma. It consists of cells similar in character and arrangement to those of normal islets. (From a specimen of Professor J. H. Biggart's.) × 5.

Cysts of various kinds may occur :—

1. **Congenital cystic disease,** either alone or associated with cystic kidney, and sometimes also with a similar condition in the liver and occasionally as part of the multiple-tumour syndrome of Lindau's disease (pp. 1131–2), has been observed.

2. **Retention-cysts,** due to obstruction of the pancreatic duct by calculi, cicatricial stenosis, pressure from without, or its involvement by malignant tumour of the head of the pancreas, or of the pylorus or duodenum, occur. In a

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[1] R. M. Wilder, M. H. Power, and H. E. Robertson, *Jour. Amer. Med. Assoc.*, 1927, **89**, 348.

case seen recently by one of the authors, a very large retention-cyst in the tail of the pancreas simulated, and was, before operation, taken to be, a considerably enlarged spleen.

3. **Hydatid-cysts** are rare, as are also the pseudocystic cavities which result from the **absorption of hæmorrhage** or **of the products of necrosis.**

DIABETES MELLITUS[1]

As this disease is intimately related to the internal secretion produced by the island-tissue of the pancreas, it should logically be considered under disorders of the endocrine organs, but it is convenient to deal with it here along with other lesions of the pancreas.

Diabetes mellitus is a disorder of carbohydrate-metabolism and is characterised by an inability to store and utilise sugar, so that it accumulates in the blood and overflows into the urine.

Carbohydrates are ingested in many forms—starch, sugars, etc.—and in the intestine they are converted into monosaccharides, glucose being the most important of these. The sugar is conveyed to the liver by the blood and there largely transformed into, and stored as, glycogen. From the liver, glycogen is issued as required, being first transformed into glucose. The muscles require glycogen for their activity and large amounts may be used up in active exercise. Glucose is also necessary for the efficient combustion of fats. For the utilisation of glucose, the internal secretion of the pancreatic islets, insulin is necessary, and it is lack of this that is the basic cause of diabetes mellitus. The islet-tissue consists of two main types of cells (p. 791) which have granules reacting differently to certain reagents, and known, respectively, as A (or α) and B (or β). Both the A and B granules are rapidly autolysed after death, so that, as pointed out on p. 791, unless the pancreas is removed immediately after death and fixed at once in the appropriate reagents (such as osmic acid and potassium dichromate), the granules cannot be demonstrated. This may account for the apparent absence of any pathological change in many pancreases removed from human cases of diabetes. Of the granules, the B type appears to be that associated with insulin ; and these granules may indeed represent, histologically, the excretory appearance of that hormone.

By complete excision of the pancreas in the dog, diabetes mellitus may be produced experimentally, but in an acute form which ends fatally in a week or two. If, however, appropriate doses of insulin are given in time, death is averted as long as they are continued.

If even only a very small amount of pancreas is left, the animal survives, and may show no disturbance of metabolism if kept on a very low diet with a minimum of carbohydrate ; but, if this diet be increased, sugar begins to appear in the urine, and, if the carbohydrate is pushed, the animal may show all the symptoms of severe diabetes and die. Examination of the portions of pancreas left behind shows that the islet-tissue is in a state of " hydropic " degeneration, especially the B cells, which appear swollen and bloated, and have lost their granules : the A-type cells may still be present. This change is due to an over-activity of the B cells, followed by their exhaustion and degeneration.

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[1] " Diabetes," from Greek, διά, *dia*, through, and βαίνειν, *bainein*, to go or pass : and Latin, *mellītus*, sweet like *mel*, honey : hence applied to this disease in which there is the " passing-through " of sugar in the urine.

In man, diabetes may be of all grades. In a moderately severe case, carbohydrate is absorbed from the intestine satisfactorily and carried to the liver, but there, owing to the deficiency of insulin, the glucose cannot be transformed into glycogen, and in consequence appears in excess in the blood. Normally blood-sugar, during fasting, ranges from 0.08 to 0.1 per cent. (80 to 100 mgr. per 100 c.cm. of blood) ; after a meal containing carbohydrates it rises to about 0.15 or 0.16 per cent. in an hour ; and by two hours it has returned to the normal level of about 0.1 per cent. In diabetes, the fasting-level is high—perhaps 0.17 or 0.20 per cent.—and therefore sugar appears in the urine—the average renal threshold being about 0.18 per cent. Following the ingestion of carbohydrate, the blood-sugar rises and maintains a high level, 0·25 per cent. or even more, for several hours, coming back slowly to its former level (Fig. 457).

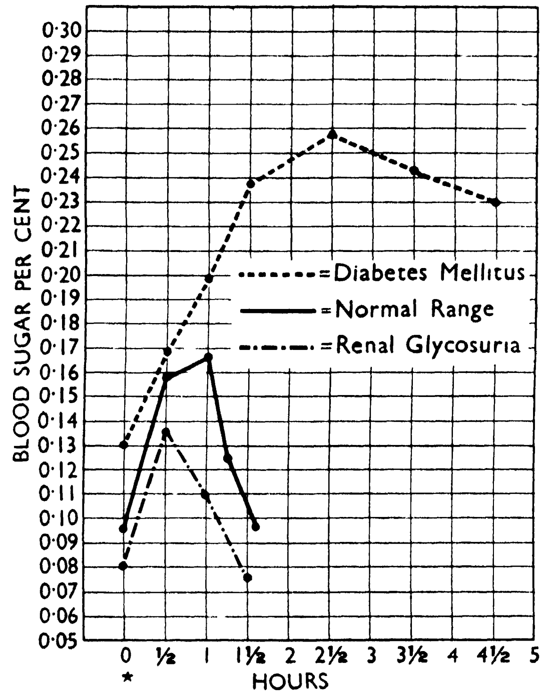

FIG. 457. *Sugar-tolerance.* Diagrammatic chart to show the blood-sugar curves following administration of 50 grammes of glucose at ★.

The fasting blood-sugar level is shown to the left. In the normal person it rises to about 0·15 or 0·16 per cent. in one hour but no sugar appears in the urine, and, in between one-and-a-half to two hours, it returns to normal.

In the diabetic, as a rule, the fasting-level is higher than normal, it rises still higher and remains elevated beyond the two-hour period. Sugar appears in the urine, or increases as compared with the fasting-period.

In renal glycosuria, the fasting level is low and sugar appears in the urine even before the normal renal threshold is reached.

In cases of severe diabetes, even the withholding of carbohydrate may fail to prevent the loss of sugar from the body. First, the glycogen of the liver is used up, then the fats, and even the proteins of the body are transformed into sugar, so that emaciation may be extreme and—unless prevented by insulin-therapy—death is inevitable.

In addition to the defect of carbohydrate metabolism, there is faulty combustion of fats in diabetes. This is one of the most serious factors in the disease as, instead of the end-products of fat-metabolism being CO_2 and H_2O, intermediate acid-bodies are formed, such as β-oxy-butyric acid and aceto-acetic acid; the latter may be further broken down to form acetone, which may be detected in the urine and the expired air. These bodies, particularly aceto-acetic acid, produce a **ketosis**[1] in the blood and require to be neutralised. For this purpose ammonia is formed in excess and the bicarbonate of the plasma has also to be utilised. Failure to neutralise the acid-bodies results in deep respirations, coma—diabetic coma—and death, if active measures are not taken at once.

There may be also an excess of fat in the blood (p. 585)—" lipæmia "—consisting of both neutral fats and cholesterol-esters, and, though the liver has no glycogen store, its cells may be loaded with fat. Fat may also be demonstrable in sections of spleen and lymph-nodes.

The injection of insulin may restore the metabolic processes to normal if the dosage is correct and it is given in time. Its action is to make possible the formation of glycogen from glucose; and, with the normal metabolism of sugar, fat-metabolism is also corrected and the ketosis disappears.

Whilst it is clear that the deficiency or absence of insulin will produce the picture of diabetes, it has been shown by B. A. Houssay and his collaborators *(1930 and later) that the features of diabetes—glycosuria, hyperglycæmia, ketosis, etc.—may be definitely lessened in the experimental animal by removal* of the pituitary. Such removal makes the animal very sensitive to insulin. *It is mentioned in discussing the pituitary's functions (pp. 806–8) that that* gland controls all the other endocrines. With regard to its relationship to the pancreas it seems to produce at least two factors, " diabetogenic " and " ketogenic " factors, which are antagonised by insulin. Therefore, when insulin is deficient, these come into play and the condition of diabetes mellitus is the result.

In contrast with Houssay's experiment, in which the dog had both pancreas and pituitary removed, it has been found by F. G. Young (*see* footnote, p. 805) that, in the dog, injections of **anterior pituitary extract** bring about a condition of diabetes. At first this is **temporary** but, if the injections are continued and increased, it **persists** and is associated with " hydropic degeneration " of the pancreatic islets.

LESIONS OF DIABETES MELLITUS IN MAN:—

Pancreas. The organ usually shows little or no change on naked-eye examination. Microscopically, no change may be demonstrable, owing, in all probability, to post-mortem autolysis having destroyed the finer cell-constituents of the islets, as already explained (pp. 791 and 800). In a small proportion of cases the islets may show (i) hydropic degeneration such as is demonstrable in the more acute lesion in the experimental animal (pp. 792–3 and 800): (ii) atrophy: or (iii) a loss of cellular character owing to overgrowth of the stroma which may be hyaline or fibrous in nature (Fig. 458).

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[1] "Ketosis," from "ketone," a variant of "acetone," from the Latin *acētum*, vinegar, from *acer*, sharp, sour, acid.

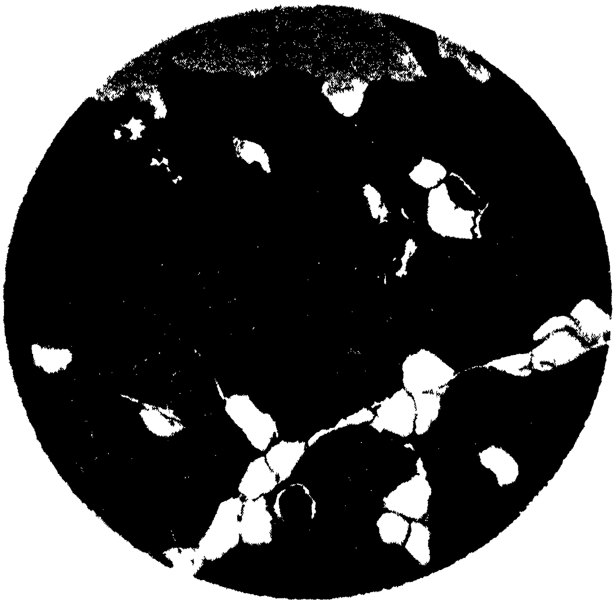

FIG. 458. *Pancreas in diabetes: hyaline islets.* The darker areas indicate the islets in which the stroma is increased and hyaline and the cells have largely disappeared. Stained by azan method. (From Dr. R. F. Ogilvie.) × 75.

If the damage to the pancreas has arisen from chronic inflammation around, or from blockage of, the ducts, there may be alterations of an atrophic and fibrotic nature in the acinar tissue, but the islet-tissue is much less affected, indeed, diabetes may not be produced, or may occur only in the later stages. Occasionally, hyperplastic changes may be found in islets which are much larger

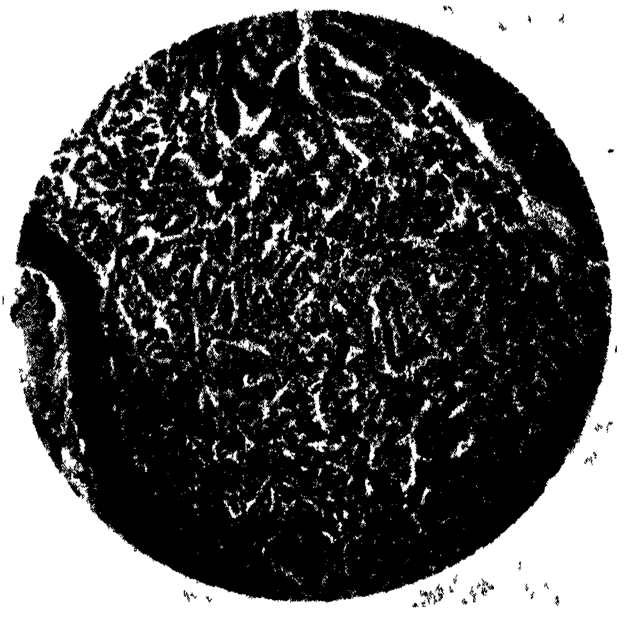

FIG. 459. *Pancreas in diabetes: hypertrophied islet.* While some islets are atrophic and hyaline, others, such as that shown here, may be greatly enlarged—a compensatory hypertrophy. Hæmatoxylin and eosin. (From Dr. R. F. Ogilvie.) × 50.

than the average and have large clear cells. A word of caution is necessary here with regard to size and number of islets. Ogilvie (1933, 1935, 1937), in examining tissue from different parts of the gland, has shown that there is a considerable variation in the normal size and number of islets, probably determined by inheritance and by age. In the newborn child of a diabetic mother, the islets are usually much larger than normal—evidently a hyperplasia which is compensatory for the maternal deficiency. Such infants may die in a state of hypoglycæmic shock within a few hours or days after birth.

Other Organs. It has already been mentioned that, in diabetic coma, there may be fatty changes in the liver-cells and in the spleen and lymph-nodes, especially if lipæmia is also present (p. 802). Such changes are to be regarded partly as an infiltration by the unused fat and partly as a result of cell-damage (*e.g.*, to the liver) from the ketosis.

The kidney frequently contains glycogen demonstrable microscopically, especially in the cells of the ascending loop of Henle, and often also in the cells of the convoluted tubules of the cortex.

Arteriosclerosis is a frequent accompaniment of diabetes and may be found even in young patients. It has the usual characters of the nodular type (atheroma or athero-sclerosis—p. 484) and may be the cause of gangrene of the extemities—"diabetic gangrene" (pp. 255–6)—or of coronary occlusion (p. 176). The explanation of the arterial degeneration is not clear, but, in addition to the liability to disturbance of the metabolism of carbohydrates and fats, the diabetic subject is very susceptible to various infections, so that his blood-vessels are exposed to damage from both sources.

This increased susceptibility to infection explains the frequency of boils and other pyogenic lesions in diabetes. The occurrence of pneumonia is a grave risk and may be complicated by gangrene of the lung. Tuberculosis is liable to develop and spread rapidly. Incidentally, it may be mentioned that, whilst insulin may obviate such risks, yet—if infection should occur—the activity of the pancreatic islets may be still further reduced and the dosage of insulin require to be increased.

The **ætiology** of diabetes is obscure. Necrosis, together with regenerative changes, may be found in the pancreatic islets in some acute infections such as pneumonia and diphtheria, and in these instances there may be some lowering of sugar-tolerance; but, in the majority of these infections, no diabetes follows. In most cases of diabetes, the onset is insidious and the disease slowly progressive, but no single factor has been found to account for the inefficiency or destruction of islet-tissue. In a few instances, gross damage to the pancreas, as by a pancreatitis or by calculi in its ducts, has been followed by diabetes. In the condition of hæmochromatosis (pp. 227, 774, 793 and 1070), with cirrhosis of the liver, the pancreas also may show a diffuse fibrosis with pigmentation, and diabetes may develop in the later stages of the disease. Because of the pigmentation, due to excessive deposition of iron in the tissues, and the accompanying diabetes, the term "bronzed diabetes" has been applied to the condition. In the arteriosclerosis complicating diabetes, the pancreatic vessels are often relatively little affected, and, conversely, in pronounced arteriosclerosis of these vessels, there may be no diabetes.

Glycosuria. This is one of the well-known signs of diabetes mellitus, but it must be remembered that sugar may appear in the urine from causes other than pancreatic disease. It may be due to increased permeability of the kidney, *i.e.*, a lowering of the renal threshold—renal glycosuria (Fig. 457, p. 801)—similar to that produced by the administration of phloridzin. The blood-sugar is lowered under such circumstances, and if insulin be administered a dangerous hypoglycæmia may result.

Injections of adrenaline (epinephrine) may cause a transient glycosuria owing to rapid mobilisation of the liver-glycogen, causing a hyperglycæmia with escape of sugar in the urine. Claude Bernard, in 1857, first showed that puncture of the floor of the fourth ventricle will produce glycosuria. This result is brought about by impulses passing down through the splanchnic nerves, and is prevented by previous section of these nerves. These impulses act partly on the liver itself, but mainly on the suprarenal cortex, leading to an increased liberation of adrenaline, which is then carried to the liver and brings about the active mobilisation of its glycogen. It has been shown by Macleod and others that insulin may minimise the effects of adrenaline and of fourth-ventricle puncture.

Asphyxia, whether produced mechanically or due to administration of anæsthetics, may cause glycosuria, again owing to liberation of liver-glycogen, apparently the result is due to anoxæmia, causing an increase in the *p*H-concentration of the blood and possibly also by producing increased enzyme-activity in the liver-cells.

In hyperthyroidism (" thyrotoxicosis "), hyperglycæmia and glycosuria are not infrequent, the action being probably through the medium of the suprarenal medulla.

References

The literature of Diabetes Mellitus is enormous, but the following special works give further references and will themselves furnish full information on this and allied subjects :

1. J. J. R. Macleod. " Carbohydrate Metabolism and Insulin." Monographs on Physiology. 1926. Longmans, Green & Co. Ltd., London.

2. E. P. Joslin, *et al.* " Treatment of Diabetes Mellitus." 1935. 7th ed., Henry Kimpton, London.

3. D. Warren. " The Pathology of Diabetes Mellitus." 1938. 2nd ed., Lea and Fibiger, Philadelphia.

4. " Glandular Physiology and Therapy." *Amer. Med. Assoc.*, 1935.

5. W. W. Payne, Great Ormond Street. " Diabetes in Children." *Brit. Med. Jour.*, 1936, **ii**, 960.

6. F. G. Young. " Experimental Investigations on the Relationship of the Anterior Hypophysis to Diabetes Mellitus," *Proc. Roy. Soc. Med.*, 1938, **31**, 1305.

CHAPTER XXIV

DISEASES OF THE DUCTLESS GLANDS—THE ENDOCRINE ORGANS :—

PITUITARY (HYPOPHYSIS CEREBRI), THYROID, PARATHYROID, SUPRARENAL (ADRENAL), PANCREAS, THYMUS, Etc.

INTRODUCTION. The lesions which occur in these organs follow the general types of pathological change—degenerations, inflammation, tumours, etc.; but the effects—"disorders" or "diseases", or, perhaps more accurately "syndromes" produced—depend on the interference with the special secretions of the organs themselves. Such interference may take the form of (*a*) reduction in normal activity, *i.e.*, *hypo*-function, or (*b*) excess of activity, *i.e.*, *hyper*-function, or possibly (*c*) perversion of function or "*dys*-function"—we apologise for employing these "hybrids"—they are convenient and in common use. The position is greatly complicated by the fact of the interrelationships of the different glands, a feature seen prominently in the case of pituitary lesions. It is sometimes possible to recognise a primary injury of one gland leading to interference with special function, whilst the same gland may be injured in a similar fashion as the result of disease of another endocrine gland.

Whilst the several endocrine glands vary greatly in structure and function, they have a common mode of action in that they produce substances—hormones—which are taken up directly by blood-vessels or lymphatics, and so introduced into the tissues and organs by the blood-stream.

In addition to the glands mentioned in the title-heading, it is now recognised that there are many other organs which, in addition to their more obvious activities, produce hormonal substances acting in a similar way through the blood-stream. Thus the testis, ovary and placenta form substances controlling growth and reproduction, and the liver, the gastro-intestinal mucosa and the kidney, and probably the bone-marrow, may be regarded as having hormonal functions.

The whole question of the physiology of this system is in a fluid state and what seem to be established principles to-day are liable to be modified to-morrow by some new advance in knowledge. A vast amount of research has been undertaken and is still in progress, with an immense amount of literature as a result. It is impossible here to attempt even a synopsis of the functions of the various organs dealt with; only brief references can be made to certain points in order to help in the understanding of the disease-processes under consideration. For fuller information special works must be consulted, *e.g.*, Sharpey-Schafer's "The Endocrine Organs" (1924), Swale Vincent's "Internal Secretion and the Ductless Glands" (1924), and the symposiums on "Glandular Physiology and Therapy," published by the American Medical Association (1935). In the last work are numerous references to the more recent work up to that date. For the biochemical mechanisms concerned, the "Annual Review of Biochemistry" should be consulted, more particularly the numbers for the last four or five years.

Of recent years the pituitary has been recognised to be the "master-gland" in the endocrine system, and for this reason it will be dealt with first.

DISEASES OF THE PITUITARY BODY

OR HYPOPHYSIS CEREBRI

The hypophysis cerebri is a small, slightly flattened, greyish-red body, which lies in the pituitary fossa or sella turcica of the sphenoid bone at the base of the skull. It consists of a larger, anterior or glandular, stomatodæal portion; in intimate relation with which lies the smaller, posterior part, which is connected with the floor of the third ventricle by a delicate, soft, easily-ruptured stalk of nervous tissue—the infundibulum. Both of these portions arise originally as hollow diverticular processes, the lumina of which, in course of time, in the human subject, usually become obliterated ; though parts of them—especially that of the glandular portion—sometimes persist, and may occasionally become distended and form cysts, the lining-cells of which may show cilia. In its phylogenesis, the gland was originally an organ which was situated at the anterior end of the central nervous canal, into which it poured its secretion. Whilst its position protects it from external injury, the fact that the gland lies in a practically closed cavity of bone and dura, surrounded by a vascular plexus, makes the pituitary liable to pressure and even destruction from hæmorrhage from its vessels, or from infection in its vicinity, or tumour of its constituent cells.

Microscopically, the **anterior lobe** consists of three types of cells in varying proportions —the **chromophobe** cells which are so called because their cytoplasm stains but faintly with the ordinary stains and contains none or only a few faintly-staining granules : the **chromaphil** cells which are of two kinds, (*a*) the oxyphil or eosinophil, and (*b*) the basiphil, so called because of the deeply-staining granules they respectively contain. These various types may be increased or diminished in disease-conditions to which reference will be made later.

The chromophobe type appears to be the undifferentiated form of cell from which the others arise and, not infrequently, both in normal and in diseased glands, intermediate forms are found. The **oxyphil** type is associated in some way with the growth-factor of the hypophysis and the **basiphil** with the sexual factors, but the details of the connection between the character of the cell-granules and the function of the gland are not yet known.

Differences are described between the Golgi-apparatus of the three types of cell. These various cells are arranged in irregular groups and alveoli which are separated by a mesh-work of capillaries communicating with the blood-vessels of the capsule and of the stalk.

Extending on to the stalk of the hypophysis is the **pars tuberalis,** a layer of cubical cells.

In the **pars intermedia,** which is often absent or but poorly developed in the human gland, there may be small acini, lined by cubical cells and sometimes containing colloid.

The **posterior lobe,** or **pars nervosa,** is composed of neuroglial fibres and scattered branching cells ; some of the latter may contain colloid droplets. There may be seen occasionally a few basiphil cells irregularly distributed in the posterior lobe.

Nerve-fibres are demonstrable in both anterior and posterior lobes and in the stalk, and by these nerve-fibres connections are made with the hypothalamic nuclei, more particularly with the supra-optic nucleus, a group of nerve-cells lying alongside the optic chiasma. This nervous connection between hypophysis and hypothalamus is important and may form one of the channels whereby pituitary hormones can act on the body-mechanisms (*see* later under Diabetes Insipidus, p. 819). If the pituitary is to be regarded as "the leader of the endocrine orchestra the hypothalamus is its conductor" ; and, just as the "translation of nervous activity into chemical mechanisms occurs at every nerve-ending throughout the body [so] we may fairly apply it to the endocrine system." In the same way "the pituitary-hypothalamus apparatus is now regarded as a unit where nervous mechanisms can be transformed into chemical ones".[1]

CONGENITAL ABNORMALITIES. The original pharyngeal epithelial outgrowth (**Rathke's pouch**), from which the anterior lobe develops, may persist as a cyst, lined by columnar, sometimes ciliated, epithelium, though flattening of this may occur from distension. It causes pressure on and destruction of the rest of the gland. (*See* later, under Hypopituitarism and Tumours, pp. 808 and 815 *et passim*, 817).

Internal Secretions produced by the Pituitary. In addition to what may be regarded as basic-function hormones, namely those controlling growth of the body generally and those concerned with reproduction, the pituitary, by means of its anterior lobe, furnishes substances which control the other endocrine organs, as well as the secretion of milk. These substances are known as thyrotropic, adrenotropic, parathyrotropic, gonadotropic, etc., as they stimulate the thyroid, adrenal, parathyroid and the genital glands respectively. It has also been shown (by Houssay and others, 1929–1933) that the anterior lobe can produce a substance (the diabetogenic substance or factor) which is capable of stimulating the liver to raise the level of the blood-sugar, and thus antagonising the action of insulin : and another substance (the ketogenic substance or factor) which can increase the ketone-bodies in the blood. The posterior lobe furnishes a pressor factor (pitressin) controlling the circulation and oxygen-consumption, and another factor (pitocin) acting on plain muscle, especially uterine muscle ; it is regarded as producing in addition a hormone controlling the metabolism of water and probably of salt (*see* Diabetes Insipidus, p. 819). The activities of the pituitary are stimulated by the injection of the œstrogens (p. 916) ; and, for the influence of the over-activity of the pituitary on the production of adenosis and tumour-formation in the breast, *see* pp. 934 and 942.

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[1] Leading article on "Endocrine Interactions," *British Medical Journal*, 1941, *i*, 755,

The pituitary is thus an extremely important controlling-centre for all bodily activities and acts either directly or by affecting the action of other endocrine organs.

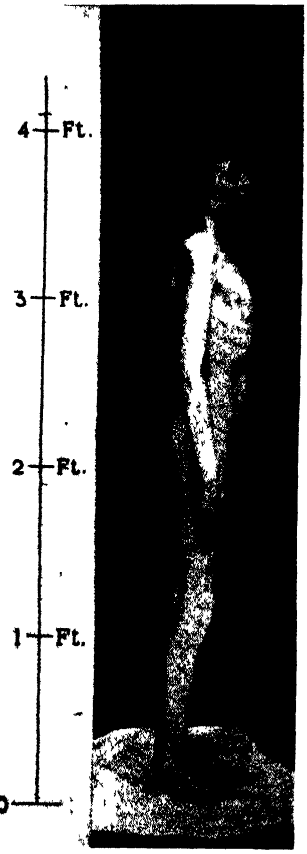

FIG. 460. Hypopituitarism of "Lorain" type associated with a pituitary cyst arising from Rathke's cleft with secondary lesions in the hypothalamus. The patient was 4 ft. 1 in. in height, weighed 47 lb. She died on her twentieth birthday. (W.E.H.)[1]

LESIONS OF THE PITUITARY AND THEIR EFFECTS

The effects of lesions of the pituitary may be to cause **Hyperpituitarism,** where one or another or perhaps several of the activities of the pituitary are increased : or **Hypopituitarism,** where the activities of the gland are decreased : or even **Apituitarism,** where function is completely lost. The first of these is commonly the result of tumour-growth or hyperplasia, the second and third are caused usually by some form of destructive lesion. Not infrequently, the earlier signs of pituitary disease are those of hyper-function, whilst, later, hypo-function supervenes. The term " dyspituitarism " is sometimes used to indicate a supposed abnormal functional activity, but as there is no real proof of this and as the pathological effects can be explained equally well under the headings mentioned, it seems unnecessary to introduce the term here.

In discussing the effects of hypophyseal lesions, it is important to remember the anatomical relationships of the organ. Owing to its close approximation to the optic chiasma and tracts, and to the hypothalamic region—with the latter it has nervous connections—lesions of the pituitary may also involve these structures.

Lesions causing **Hypopituitarism,** or even **Apituitarism**—are damage to, or destruction of, the gland by : (*a*) hæmorrhage from the vascular plexus surrounding it : (*b*) thrombosis or embolism in the vessels of the gland ; both of these occurrences may be found as a complication of pregnancy or the puerperium (Fig. 461, p. 809) : (*c*) infection, due to extension from meningeal infection, from adjacent bone, or from pyæmic abscess in the gland itself; (*d*) tumour of chromophobe type of cell; tumours of eosinophil and basiphil cells may later destroy the gland and metastases of other tumours may be found which cause destruction of the gland-tissue: (*e*) cystic growth, arising usually from remains of Rathke's pouch—this may occur in childhood: (*f*) compression by tumours of neighbouring structures, especially of the meninges or floor of the third ventricle.

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[1] An account of this case was published by Worster-Drought, Carnegie Dickson and Crowhurst Archer in *Brain*, 1927, **50**, 704.

The effects of such lesions vary. Sudden destruction of the whole gland, *e.g.*, from hæmorrhage, may cause coma and rapid death. Acute infection of the gland may be part of a general infection the effects of which at first overshadow the pituitary damage; but, if recovery from the general infection takes place, the effects of pituitary damage may persist. Where a chromophobe-tumour grows from the cells of the pituitary it may, by extension upwards towards the brain, produce the symptoms of intracranial pressure before any hypopituitarism is noticeable.

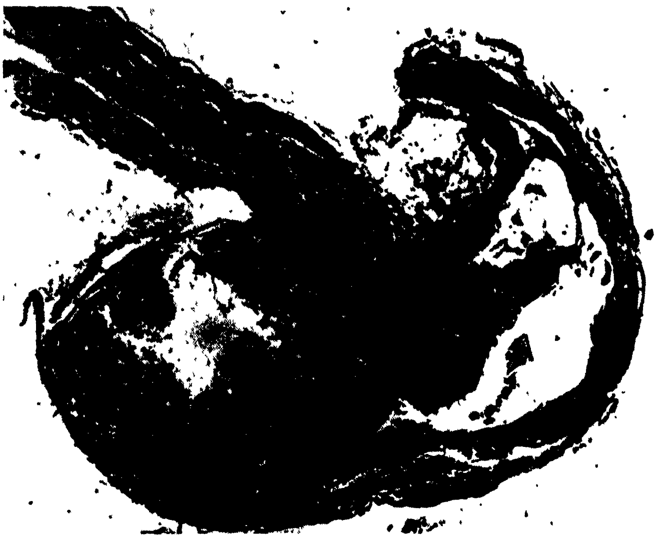

FIG. 461. Pituitary, from a case of Simmonds' disease, showing extensive destruction of anterior lobe (to right). From a woman, aged sixty-one, who developed symptoms at age thirty-seven following birth of child. (From Professor J. H. Biggart.) × 10.

If the victim is a child, in whom the causal lesion is frequently a cyst of Rathke's pouch, bodily growth is arrested and development ceases, and in time the appearance of the child becomes like that of an elderly person (progeria) or, in some instances, like that of a "miniature adult" (Fig. 460). There may be diabetes insipidus (p. 819). The pituitary itself may be distorted, stretched or flattened by pressure and the number of cells of all types in the anterior lobe be greatly reduced; the posterior lobe also may be crushed and atrophied. It may be noted that results similar to these can be produced by the pressure from above of a distended infundibulum in cases of internal hydrocephalus (p. 989).

In the event of an adult suffering pituitary damage, *e.g.*, as a result of hæmorrhage or thrombosis, a process of gradual regression of all activities and function ensues, and death may follow from general cachexia. This condition, seen most often in middle-aged multiparæ, has been termed **Simmonds' disease,** after Simmonds of Hamburg, who first drew attention to the syndrome in 1914.[1] The pituitary will show a loss of substance and alteration in shape, the degree depending on the amount and cause of the destruction (Figs. 461–2); often areas of scar-tissue are left containing small groups of anterior-lobe cells. All the other endocrine glands, including the gonads and suprarenals (p. 842), show atrophy with a general reduction in size and number of their cells. The naturally-occurring lesions of the pituitary may thus reproduce the condition of "panhypopituitarism" or "apituitarism" and the effects of experimental removal of the gland

Where, in addition to the pituitary lesion, there is also damage to the hypothalamic region of the brain, a condition of general adiposity may be added to the arrest of development, or atrophy, of the gonads. The clinical picture is known as **Fröhlich's syndrome.**[2] Experimentally, a similar arrest of growth and sexual atrophy with adiposity has been produced, where hypophysectomy was performed and where the hypothalamic region of the brain was damaged.[3] Hypoglycæmia may be present owing to the absence of, or diminution in, the anti-insulin factor.

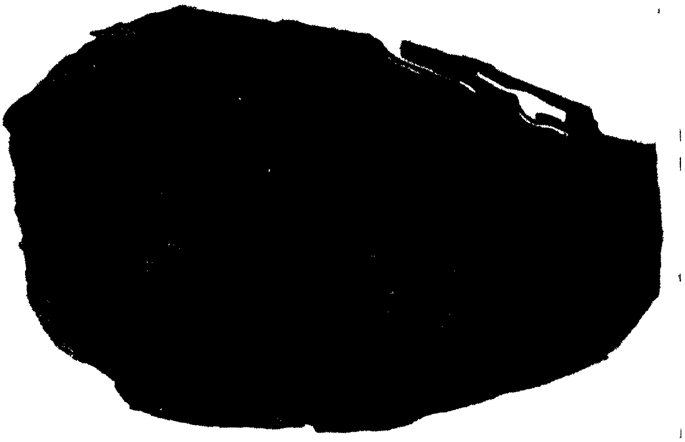

FIG. 462. *Syphilitic disease of pituitary.* In the anterior lobe are two rounded areas where the gland-tissue is replaced by gummatous formation. In the rest of the pituitary are pale patches of fibrosis. From a syphilitic patient with symptoms suggesting the early stage of Simmonds' disease. × 9.

Hyperpituitarism. The most obvious feature of this state is excess of growth brought about by the excess of the growth-hormone. In the human subject, hyperpituitarism may be manifest as a state of **Giantism** (or **Gigantism**), in which the growth-stimulus has occurred in early life before the ossification and union of the epiphyseal cartilages is complete. The experimental parallel of this is seen in rats in which normally there is no union of epiphyses; when these animals are treated with anterior-lobe extract, continuous growth in length is possible. In giantism, there is general increase in bulk of all the tissues and size of viscera as well as increase in general height. Such giants may, at first, maintain their development, but, later, tend to become enfeebled and die owing to subsequent changes of a destructive character developing in the pituitary itself. They may, on the other hand, pass on to the state of acromegaly.

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[1] *Deutsche med. Wochenschr.*, 1914, **40**, 322.

[2] *See* Fig. 462A in Appendix, p. 1256.

[3] *See* Fig. 462B in Appendix, p. 1257.

ACROMEGALY was first recognised as a separate disease in 1886 by Pierre Marie,[1] who distinguished it from such conditions as myxœdema, osteitis deformans, and leontiasis ossea. In contrast with giantism, it supervenes after the ossification of the epiphyseal cartilages, hence the growth-effects are modified. It is characterised especially by **enlargement of the extremities**—hands, feet, and certain parts of the head (Figs. 463–4–5)—the increase being not only in the bones, but also in the overlying soft parts. The increase of the hands and feet is in breadth and thickness rather than in length, the fingers being clumsy and sausage-shaped, and the great toe usually markedly enlarged in proportion to the other toes. The forearms and legs are, as a rule, not specially increased. The bones of the skull, and especially those of the face, particularly the jaws, are enlarged, the lower jaw being usually most affected, and often elongated and projecting much beyond the upper, so that the teeth

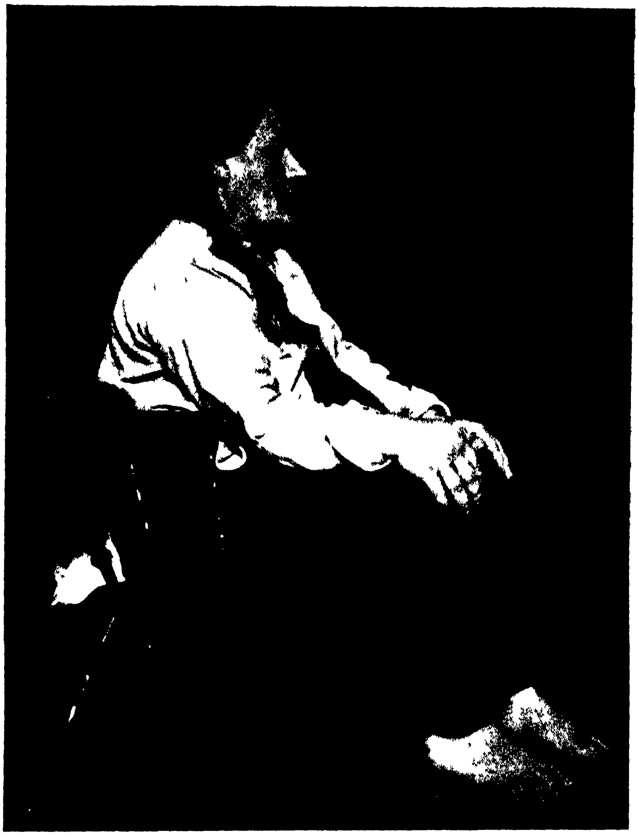

FIG. 463. *Acromegaly.* Typical case showing the characters described in the text. Note especially the enlargement of hands and feet, the large coarse features of the face, etc. (A case of the late Professor Greenfield, R.I.E.)

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[1] *See* footnote on p. 1075.

[2] Hence the name "Acromegaly," from Greek *ἄκρον*, *akron*, a point or extremity : and *μέγας*, *μεγάλη*, *μέγα*, *megas*, *megalē*, *mega*, large.

cannot be approximated, The bony prominences and ridges are exaggerated, often asymetrically, and the skull comes to resemble somewhat that of a gorilla. The ears and eyelids, the nasal bones and cartilages, and the lips and tongue, are increased in size and thickness ; and these various changes, together with the thick, coarse character of the skin, produce a characteristic picture. The skin often shows numerous warty excrescences and pigmented moles, and the hair is long and coarse. The spinal column frequently shows kyphosis (p. 1219) or other type of curvature (Fig. 464, A) ; and the ribs, sternum, and pelvis are usually enlarged and thickened. The abdomen is often protuberant, and many of the internal organs, *e.g.*, the stomach, may show great enlargement—the so-called "splanchnomegaly ".

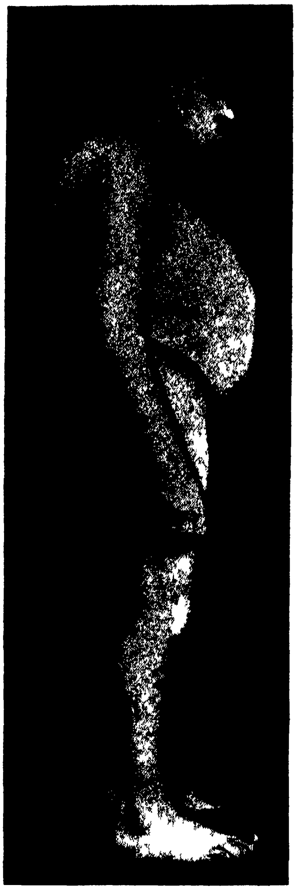

FIG. 464 (A). Acromegaly in a man aged 28, showing kyphosis of the thoracic, and lordosis of the lumbar, regions of the spine. (*See also* X ray photograph, Fig 465.) (W E H. case, by courtesy of Dr. Yealland.)

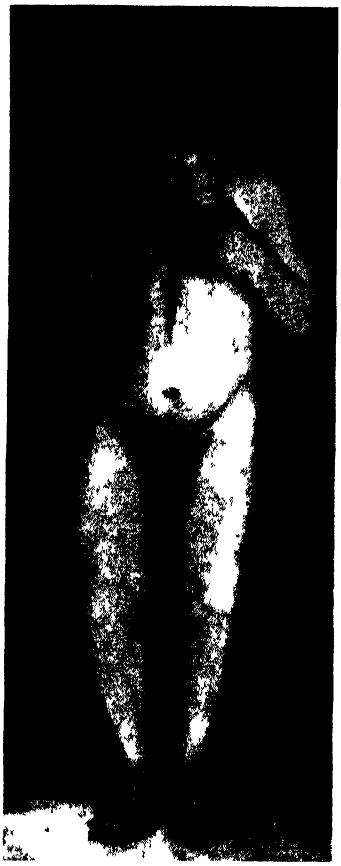

FIG. 464 (B). Acromegaly in a man aged 50, showing enlargement of hands and feet, etc. (W.E.H. case, by courtesy of Dr. Worster-Drought.)

During life, glycosuria and hyperglycæmia are both frequently found, in contrast to hypopituitarism, where hypoglycæmia is present. There may be symptoms related to the enlargement of the pituitary, such as bitemporal hemianopia and headache. As the disease progresses, symptoms of hypopituitarism (p. 808) usually supervene.

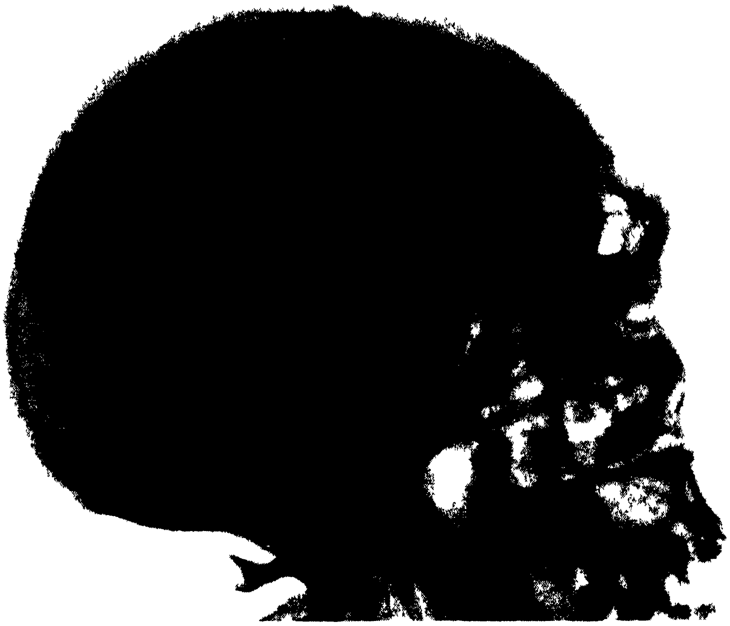

FIG. 465. *Acromegaly, pituitary tumour.* X-ray of skull showing enlargement of pituitary fossa. Male, aged 28 years (*see* Fig 464A). (W.E H.)

Examination of the pituitary shows an increase in the eosinophil type of cell, either in the form of a general hyperplasia or, more commonly, in localised tumour-fashion (Figs. 467–8, p. 814). These eosinophil cells increase at the expense of those with basiphil granules, but there is often, in addition, an

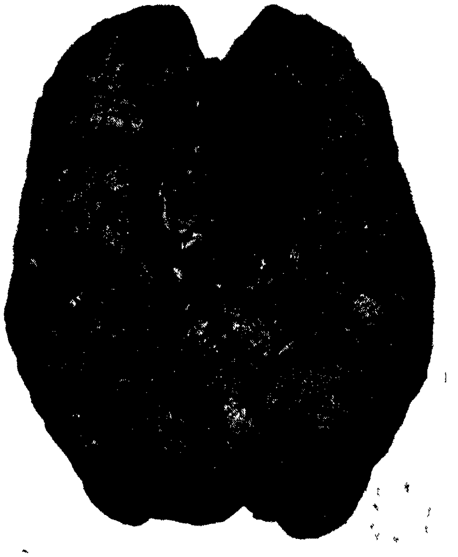

FIG. 466. *Acromegaly. Large eosinophil adenoma of pituitary* (*cf.* Fig 467). The tumour has indented the brain and compressed and destroyed the optic chiasma and nerves. From a male, aged forty-five, whose symptoms began at age twenty eight and latterly they included fronto occipital headache, blindness and polyuria. (By courtesy of Medical Staff of Lambeth Hospital.)

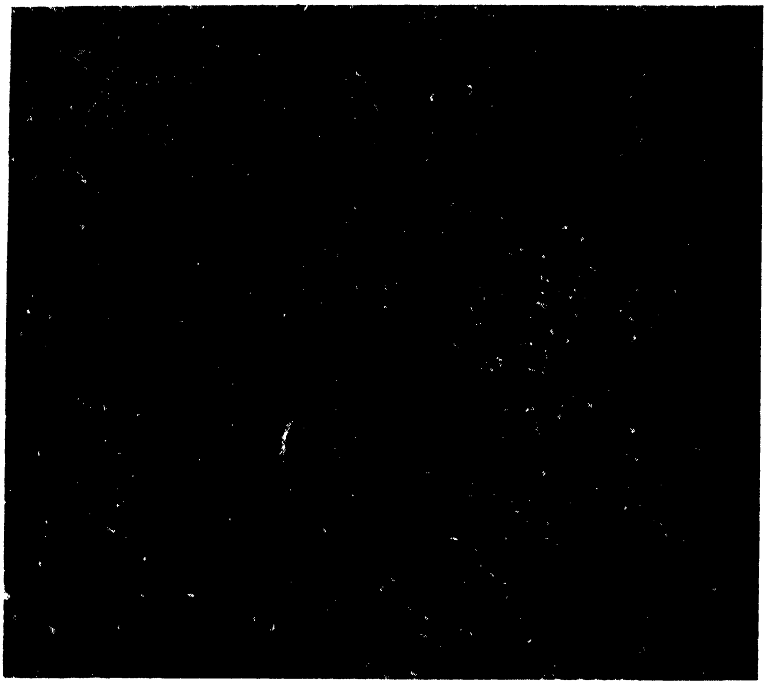

FIG. 467. *Acromegaly. Eosinophil adenoma of pituitary.* There is a diffuse growth of the eosinophil cells with little supporting stroma and a few small blood-vessels. From the same case as Fig. 466. (Lambeth Hospital case.) Hæmatoxylin and eosin. × 100.

increase of the chromophobe cells, or cells showing only few eosinophil granules ; the stroma of the eosinophil adenoma is scanty and consists mainly of blood-capillaries between the cells. The enlargement of the gland is gradual, and, as a result, the pituitary fossa becomes expanded, a feature which may be

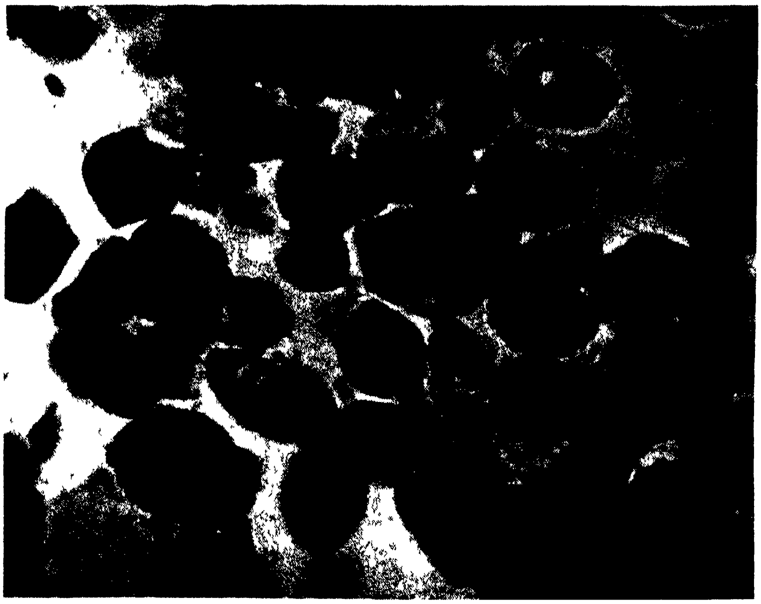

FIG. 468. *Acromegaly. Eosinophil adenoma of pituitary..* All the darkly-stained cells are eosinophils ; a few pale—chromophobe—cells are present amongst them. Eosin-pyrrol blue stain. (From Professor J. H. Biggart.) × 900.

discernible by radiographical examination and which is of value in diagnosis (Fig. 465).

If the enlargement is neoplastic in nature, the mass may spread beyond the confines of the fossa and extend upwards to indent the brain, and forwards and laterally to press upon the optic chiasma or optic tracts (Fig. 466).

The continued growth leads usually to compression and degenerative changes—necrosis, hæmorrhage, etc.—in the tumour itself. Thus, what had been at first an example of hyperpituitarism becomes later one of hypopituitarism. The glycosuria of the earlier stage is evidently the result of excess of the diabetogenic factor. Polyuria may develop as the pituitary becomes destroyed, or if the hypothalamic region is encroached upon (*see* Diabetes Insipidus, p. 819).

Experimentally, by injections of anterior-lobe extracts, structural changes approximating to those of human acromegaly with glycosuria and hyperglycæmia have been produced in dogs.

Basiphil Adenoma of Pituitary (with the production of Cushing's Syndrome).[1] Harvey Cushing of Boston, in his monograph on the Pituitary (1912), first called attention to a peculiar train of symptoms which were subsequently identified as being associated with and caused by an excess of basiphil cells in the pituitary, in the form of an adenoma (Figs. 470, 471). The striking feature of the condition is that, although this adenoma may be of minute size (perhaps only some 2 to 5 mm. in diameter), and may be overlooked unless serial sections of the pituitary are made, the symptoms associated with its presence are severe and disabling. Briefly, they consist in progressive and painful obesity with stretching of the skin, a hyperæmic condition of the face and frequently general cutaneous purpuric hæmorrhages, marked hypertension with cardiac hypertrophy, sometimes glycosuria, not infrequently softening of the bones with bending of the spine and spontaneous fractures and, especially in females, hypertrichosis. In the female, amenorrhœa develops and in the male there may be impotence and testicular atrophy. The victims of this disease become progressively weaker and frequently die from some intercurrent pyogenic infection. Cushing (1932, *loc. cit.*)

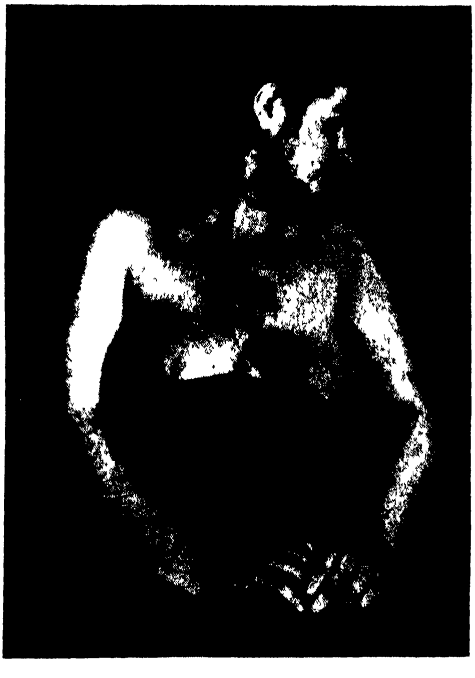

FIG. 469. "*Basiphil pituitary syndrome*" of Cushing in a female aged 25, with hirsuties, high blood-pressure, headache and visual disturbances. Wassermann and Kahn reactions negative. R.b.cs. 6,150,000, w.b.cs. 14,200 per c.mm. Hb. 102 per cent. Colour-index 0·83. X-ray of pituitary fossa: "clinoid processes rather approximated." (Dr. W. R. Reynell's case, W.E.H.)

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[1] *See* Papers relating to the Pituitary Body, etc., by Harvey Cushing, *e.g.*, on "Pituitary Basophilism," *Johns Hopkins Hosp. Bulletin*, 1932, **50**, 137 : and *Arch. of Internat. Med.*, 1933, **51**, 487.

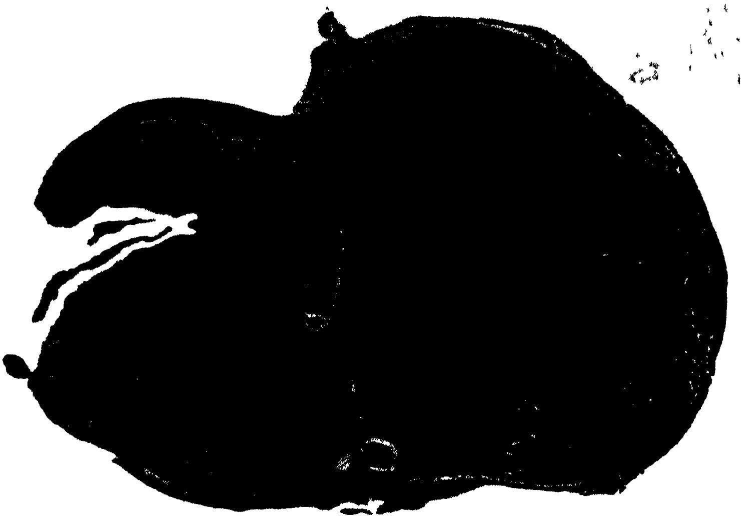

FIG. 470. *Basiphil adenoma of pituitary.* In the anterior lobe (to right) is a small ovoid well-defined tumour, composed of basiphil cells. From a female, aged thirty-five, who exhibited Cushing's syndrome. (From Professor J. H. Biggart.) × 8.

records a case of what appeared to be spontaneous recovery and he also instances others in which the disease seemed to be arrested by radiotherapy.

In addition to the adenoma in the pituitary, the changes in the organs are those of hypertensive arteriosclerosis. There are no uniformly constant

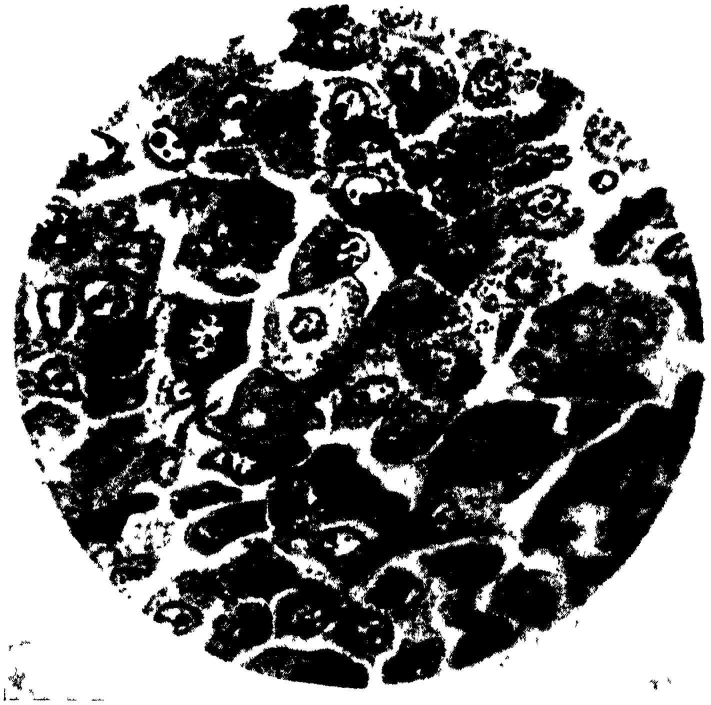

FIG. 471. *Basiphil adenoma of pituitary.* Some cells are filled with basiphil granules, others exhibit granules in all stages of transition from faintly stained to fully coloured. Drawing of a section stained by acid-fuchsin pyrrol-blue. (From Professor J. H. Biggart.) × 900.

findings, but hypertrophy of the suprarenal cortex has been observed in some cases, atrophy of ovaries in others, and rarefaction of bones in several. Many of the findings in this disease resemble those produced by suprarenal cortical tumours (pp. 847–8) and the true nature of the condition may require for its identification the detailed and minute histological examination of the pituitary. While there seems no doubt as to cause and effect between the basiphil adenoma and the clinical syndrome, the exact mechanism is obscure. There is a relative increase of the numbers of the basiphil cells in the pituitary after the menopause or after removal of the ovaries in the female, and after castration in the male. There is also a characteristic vacuolation in the basiphils under these circumstances and in cases of prostatic hypertrophy. Experimentally, the pituitary of the castrated rat shows an excess in the number of large basiphil cells showing vacuolation, and has an increased content of gonadotropic hormone. Cushing described an invasion of the posterior lobe by basiphil cells in conditions of vascular hypertension, but Biggart [1] could not confirm this.

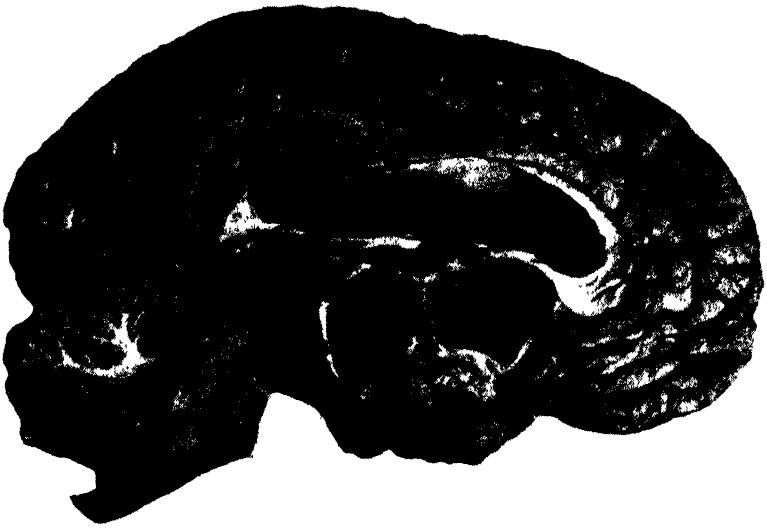

FIG. 472. "*Craniopharyngioma*" : a large suprasellar tumour, partly cystic, partly solid (for histological structure *see* Fig. 190, p. 350 : and *cf.* Fig. 473, p. 818), replacing the hypothalamic region, with obliteration of the third ventricle and sella and disappearance of the pituitary. The opaque whitish appearance of the tumour below the two large cysts is due to *accumulations of cholesterol.* The patient was a boy of fifteen years, adipose, with retarded sexual development and gradual loss of vision. (Dr. Neill Hobhouse's case, W.E.H.)

Other Tumours of Pituitary. In addition to the eosinophil and basiphil adenomas already described, **the chromophobe adenoma** is not infrequent. It may reach a large size, destroying the pituitary and invading the adjacent brain. The effects are mainly those of intracranial pressure such as may be caused by other cerebral growths, and the effects of pituitary destruction are usually overshadowed thereby. The arrangement of the cells is in solid columns or sheets held in a loose and scanty stroma, although locally invasive metastases do not occur.

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[1] *Edin. Med. Jour.*, 1935, **42,** 113.

Epidermoid Tumours ("Craniopharyngiomas"). These arise either in the gland and therefore within the pituitary fossa, or from the stalk, and are then above the fossa—"suprasellar." They are found more especially in youth or early middle age. As they are found frequently in association with the pars tuberalis they may arise from a metaplasia of its cells. They may be solid or cystic, the latter being the commoner: or a mixture of both; and are composed of squamous cells and may even show a certain degree of cornification (Figs. 472–3). Some resemble the basal-cell type of epidermoid tumour. Degenerative changes and calcification in their fibrous stroma may occur and make them identifiable by X-ray examination. A certain number of these closely resemble an adamantinomatous tumour (pp. 308, 7 (1), (i.), 350 and 707) and have been described as an ectopic variety of it. In the cystic form, there may be a papilliform projection of epithelial cells from one side of the cyst. The effects are related to their anatomical position, hence pressure on the pituitary, hypothalamus and the optic chiasma is frequent. Any of these epidermoid cystic tumours may come to contain accumulations of **cholesterol-crystals** and form the commonest variety of so-called intracranial **cholesteatoma** (Fig. 472).

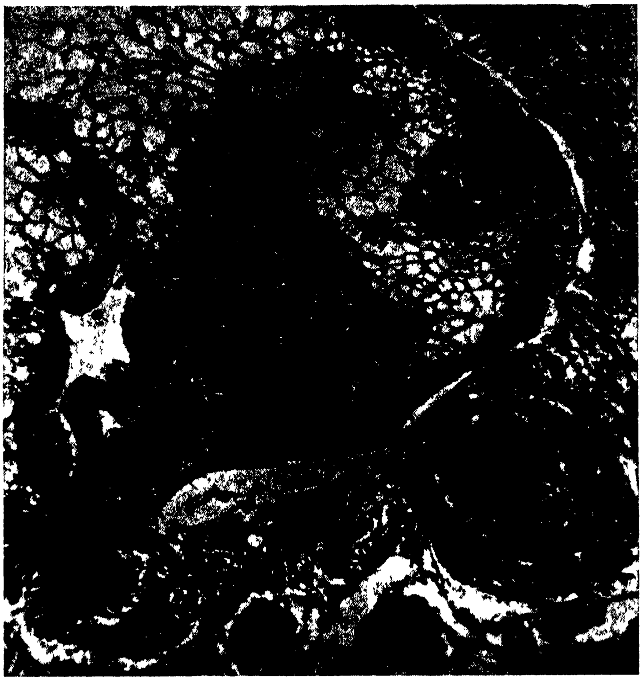

FIG. 473. "*Craniopharyngioma*" *of pituitary region.* From a case similar to that shown in the previous Fig. 472. The epidermoid structure is seen in the form of rows and whorls of epithelial cells of squamous type; these areas, together with the loose structure of other parts, produce a resemblance to the adamantinoma (tooth-germ tumour). Several areas of calcification (black) are seen in the tumour-tissue. Hæmatoxylin and eosin. (From Professor J. H. Biggart.) × 100.

Cysts of Rathke's pouch have already been mentioned (pp. 807–9). They are often confused with the epidermoid tumours just described above, and may produce severe damage from compression of the pituitary.

Metastases from malignant tumours elsewhere may be found in the pituitary, which may also be involved by neoplasms in its neighbourhood such as glioma of the optic chiasma, tumours of the floor of the third ventricle, meningioma of the adjacent meninges, and chordoma arising in the basi-sphenoid bone: and occasionally by aneurysms of the basal vessels.

DIABETES INSIPIDUS [1]

This is a condition where a great excess of watery urine of low specific gravity is excreted by the kidneys. It is convenient to discuss it here, as it occurs frequently in destructive lesions of the pituitary and because the pituitary is the source of the anti-diuretic factor or hormone. This hormone has been regarded as a product of the posterior lobe (pars nervosa) and extracts of the posterior lobes of animals are used therapeutically when an anti-diuretic effect is desired. Histologically there seems little basis for the hypothesis of such production of a potent hormone, as the lobe consists largely of neuroglial tissue (p. 807). It seems not improbable that the cells of the anterior lobe, especially those of the pars tuberalis carried on to the infundibulum, or of the pars intermedia in animals, are the real producers of this anti-diuretic hormone, while the posterior lobe is merely a form of storehouse or sponge soaked in hormone.

While it has been shown experimentally, by Starling and Verney (1925), that the anti-diuretic hormone can act on the isolated denervated kidney, there is, from study of lesions in the human subject, considerable evidence that the hormone, produced in the pituitary, acts through the medium of, and is controlled by, the hypothalamic nuclei. There is an intimate connection between the pituitary and these nuclei by means of a vascular plexus, whilst, in addition, nerve-fibres pass between the supra-optic nucleus and the posterior lobe and pars tuberalis. If a lesion, *e.g.*, a secondary growth of tumour or a patch of encephalitis, destroys the hypothalamic nuclei, diabetes insipidus develops and does not react to injections of pituitrin, because the effector mechanism is absent. If the damage is in the pituitary itself, or in the stalk, diabetes insipidus occurs because of the interruption of nervous stimulus to produce pituitrin; but, because the nervous effector mechanism in the brain is still intact, pituitrin-injections will control the excessive diuresis.

For the **Laurence-Moon-Biedl Syndrome,** in which the hypothalamus is probably involved, *see* p. 1259 in Appendix.

DISEASES OF THE THYROID GLAND [2]

Synopsis of the Structure and Function of the Thyroid

The gland is relatively larger in women than in men. It undergoes rapid enlargement at **puberty,** and temporary alterations in its size are common, for example, enlargement at the menstrual periods and during pregnancy. It becomes relatively atrophied in old age.

The human thyroid is composed of a **lateral lobe** on each side, joined by the **isthmus.** The latter varies greatly in size in different individuals, and may in some cases be absent —a condition which is normal in certain animals, *e.g.* the sheep, in which the thyroid is therefore a paired organ. **Prolongations** of the glandular substance may be found passing upwards—or more rarely downwards—usually from the isthmus near the middle line. **Developmentally,** the thyroid arises from three independent rudiments—paired **lateral rudiments,** one on each side, which originate from the pharyngeal hypoblast of the fourth visceral cleft, and a **median rudiment** in the form of a diverticulum from the ventral wall of the pharynx. The last of these grows downwards, and its lower end bifurcates to join the two lateral rudiments. This diverticulum at first possesses a lumen, passing from the foramen cæcum at the root of the tongue above, to the isthmus below, and constitutes the **thyroglossal duct,** which, under normal circumstances, becomes obliterated and forms a fibrous cord. In rare instances, portions, or even the whole, of this duct may remain patent, and cystadenomatous and other tumours sometimes arise from it. Occasionally, accessory thyroid tissue, which may give rise to tumour-growth, is found ; this may arise from misplaced developmental thyroid buds or from the post-branchial body—a structure arising from the fifth branchial cleft and normally leaving no trace in the adult.

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[1] *See* "The Hypothalamus," by W. E. le Gros Clark, John Beattie, George Riddoch and Norman M. Dott, Henderson Trust Publication, by Oliver & Boyd, Edinburgh, 1938, and "Diabetes Insipidus," by J. H. Biggart in *Brain*, 1935, **58,** 86, and *Edin. Med. Jour.*, 1936, **43,** 417.

[2] For further details see Cecil A. Joll, "Diseases of the Thyroid Gland," 1932, Heinemann, London; A. Crotti, "Thyroid, Parathyroids and Thymus," 1938, 3rd ed., Henry Kimpton, London; and "Glandular Physiology and Therapy," 1935, published by *Amer. Med. Assoc.* References to the earlier literature are given in these works.

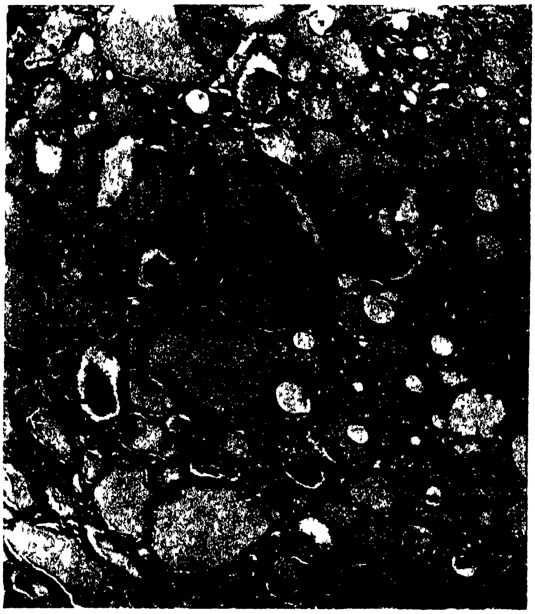


Fig. 474. Section of normal thyroid of adult. × 50.

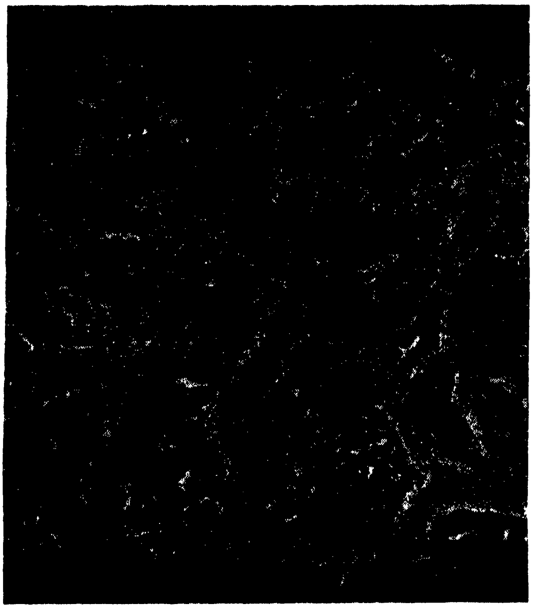


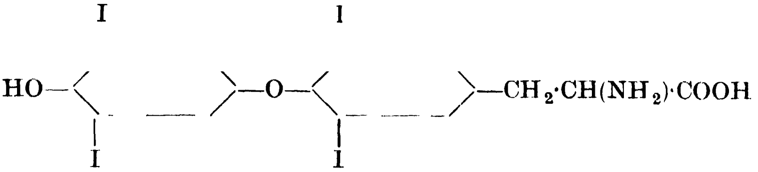
Fig. 475. Section of normal thyroid of infant. The interlobular septa are relatively thick and the acini are small and have little or no content. × 100.

Structure of the Thyroid Gland The organ is covered by a thin, dense, fibrous **capsule,** prolongations of which pass in as septa, dividing the gland into lobules, and containing blood-vessels and numerous lymphatics. The **blood-supply** of the gland is very abundant in proportion to the size of the organ ; and the amount varies with its activity. **On microscopical section,** the glandular tissue is seen to be composed of **cystlike spaces**—the largest of which may be just visible to the naked eye. They are lined by **low columnar, cubical,** or, in inactive glands, by comparatively **flattened epithelium** ; and are filled with "**colloid**" material (Fig. 474) These cystlike spaces are sections of minute closed vesicles and are surrounded by a plexus of blood-capillaries.

THE SECRETION OF THE THYROID GLAND :—

The essential thyroid hormone, usually referred to as **thyroxin,** is produced by the cells lining the gland-acini and is normally stored in the colloid-content of these acini, the colloid itself being a globulin. Depending on the needs of the body, this colloid hormono-content is absorbed in greater or lesser amount, but there is usually a reserve available in the acini. In states of hyperactivity there may be little or no colloid and the acinar content may be mucoid or may even disappear. In such circumstances the hormone may be rapidly absorbed directly into the blood.

The hormone has been isolated and also prepared synthetically by C. R. Harington and G. Barger.[1] It consists of two benzene-rings to which are attached four atoms of iodine, with an amino-acid group. Graphically it is represented thus :—



Para-hydroxi-phenyl ether of tyrosine with four iodine atoms.

The iodine is an essential element in this substance and is firmly bound to the rest of the molecule. The thyroid is the only organ that contains iodine in any appreciable quantity and the gland is capable of taking up iodine very rapidly and building it into the hormone-molecule. While not all the iodine in the thyroid is in the form of fully-formed hormone, the total iodine-content serves as an approximate index of the hormonal content and in estimating the functional state of any given thyroid gland the iodine-content is as important as the histological structure. Generally speaking, the iodine-content is higher in the colloid phase than in the actively secretory or hyperplastic phase (*see* later, under Goitre, p. 823). Marine and Lenhart [2] give the following figures for man : normal, 2·17 : hyperplastic stage, from 0·88 to 0·32 : colloid or resting stage, 2·00. The figures are iodine in milligrammes per gramme of dried gland. As the normal average human thyroid weighs from 20 to 30 grm., the total iodine-storage in the average gland may range from about 10 to 25 mgr. The importance of iodine in relation to goitre will be discussed later (p. 823 *et seq*).

The function of the thyroid hormone is to maintain the metabolic rate at an adequate level. Increase of thyroxin raises the basal metabolic rate, as in the various thyrotoxic states ; decrease depresses this rate, and also the cholesterol-level in the blood, as in myxœdema and cretinism. Thyroxin acts ultimately by increasing the oxygen-consumption and carbon-dioxide production by the cells of the body. The exact manner in which it exerts this influence is not yet known.

Relation of the Thyroid to other Endocrine Glands. The pituitary is the controlling agent of the thyroid activity by means of its thyrotropic hormone which is produced by the oxyphil (or eosinophil) cells of the anterior lobe. Experimental removal of the pituitary leads to thyroid atrophy and a similar relationship obtains in Simmonds' disease (p. 810). Injection of extracts of anterior pituitary leads to hypertrophy of the thyroid, with hyperplasia of its cells and loss of colloid and of iodine-content, the basal metabolic rate is increased, and exophthalmos may sometimes develop (*see* Exophthalmic or Toxic Goitre, p. 827 *et seq.*).

The various reactions in the thyroid that occur in goitre (p. 823) are probably initiated through the medium of the pituitary.

There is an interaction between thyroid and gonads, probably by way of the pituitary. As already mentioned (p. 819) the thyroid enlarges at puberty, at menstruation and during pregnancy. Experimentally, œstrogenic substances stimulate or depress thyroid activity, depending on the dosage used.

Thyroid hormone increases the sensitivity of the tissues to the action of adrenaline and its effect seems to be inhibited by the suprarenal cortex.

CONGENITAL ABNORMALITIES :—

Congenital absence, or athyrea, is a rare anomaly ; when it occurs, cretinism of the sporadic variety results (*see later*, p. 833 *et seq.*).

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[1] *Biochem. Jour.*, 1926, **20,** 300, and 1927, **21,** 169 ; see also C. R. Harington, " The Thyroid Gland : Its Chemistry and Physiology," 1933, Oxford Univ. Press, London.

[2] *Arch. Int. Med.*, 1909, **3,** 66.

Accessory, or aberrant, thyroids are not uncommon. They are usually small in size but may undergo pathological enlargement as aberrant goitres, or become malignant. Usually they are to be found along the line of the thyroglossal duct and, therefore, may be present anywhere between the base of the tongue and the isthmus of the gland. Sometimes they lie laterally and unattached to the lateral lobes—in this situation they must not be confused with the parathyroid glands (p. 837). Occasionally, aberrant thyroid tissue is found along the trachea within the thorax.

Thyroglossal Cysts. These arise from the thyroglossal duct and are median. They may be at the base of the tongue : above, below, or even in, the hyoid bone : or in front of the thyroid cartilage. They are lined by epithelium, usually columnar, sometimes ciliated, though metaplastic changes may give a stratified squamous epithelium. The content is thick mucus. Inflammatory changes are frequent and may destroy the lining-cells.

Atrophy. A varying degree of this is a normal senile change. The size of the acini is diminished and the epithelium becomes flattened, the colloid content is reduced, and is often dense in consistence. Atrophy is seen in Simmonds' disease (p. 810) from loss of pituitary influence. It may also supervene as a secondary change in various forms of goitre (pp. 823 and 830 *et seq.*).

Hypothyroidism follows as the effect of atrophy and is responsible for the appearance of myxœdema (pp. 833 *et seq.*).

Amyloid degeneration is occasionally found. It occurs under the usual conditions, and shows the usual characters of the disease elsewhere (p. 208).

INFECTION AND INFLAMMATORY CHANGES :—

Acute Thyroiditis. A suppurative variety of this is seen in pyæmia in which minute abscesses may be found in the thyroid as in other organs. Larger abscesses are uncommon. Non-suppurative thyroiditis is a rare condition, but has been recorded as an accompaniment of many of the acute infections, *e.g.*, scarlet fever and other acute exanthemata, typhoid (sometimes with abscess-formation), etc. In this acute inflammatory condition, the gland is swollen and tense from congestion, œdema of the interstitial tissue and leucocytic infiltration. The colloid undergoes absorption and the epithelium of the acini becomes hyperplastic and may be shed into the lumina. Some degree of thyrotoxicosis (pp. 827 and 830) may be present and certain examples of exophthalmic goitre appear to date their occurrence from such an acute thyroiditis.

In many acute infections, the thyroid may undergo " toxic " changes similar to those seen in other parenchymatous organs such as liver and kidney. The acinar epithelium may be shed or may proliferate, whilst the colloid contents are thinned and absorbed in varying degree.

Chronic Inflammations. In generalised miliary **tuberculosis,** there may be a few scattered tubercles throughout the gland. Larger tuberculous nodules are rare. Definite local manifestations of **syphilis** are uncommon in the thyroid ; gummata may occur or a more diffuse interstitial fibrosis, the latter being found occasionally in congenital syphilis. **Actinomycosis** is still rarer ; in one case, recorded by Jell, a thyroglossal cyst was the site of infection.

Under the heading of chronic inflammation may be placed the rather uncommon malady of **Riedel's Struma.**[1] The ætiology of this is unknown, some examples are probably end-results of the so-called lymphadenoid goitre (pp. 830–1), and are to be regarded, therefore, as examples of atrophy with replacement-fibrosis. In others, no traces of such antecedent condition are recognisable. The condition is sometimes called "woody thyroid," or "ligneous thyroiditis," because of the density and hardness of the affected gland. The disease usually arises insidiously and progresses slowly; and it may extend beyond the thyroid to the adjacent muscles or carotid sheaths, binding these and the thyroid together in a firm fibrous mass. Clinically, the diagnosis between this condition and malignant disease of the thyroid may be difficult. Riedel's struma may be unilateral at first and spread later to involve the isthmus and opposite lobe, or it may be more generalised from the commencement. The affected part may not be much enlarged, but is hard and smooth or slightly nodular on the surface. The acinar tissue may be completely replaced by dense, often hyaline, fibrous tissue containing few vessels and sometimes showing scattered small collections of lymphocytes. Any acinar tissue that remains is surrounded by this fibrous mass and is in process of being strangled by it; there may be attempts at regeneration in local patches of the surviving acinar epithelium. The functional effect of this sclerosis is usually hypothyroidism, and definite myxœdema may develop if the acinar tissue is extensively destroyed.

GOITRE

The term "goitre"[1] is applied to enlargement of the thyroid from any cause, but is also used in a more specific sense for those enlargements due to hyperplastic overgrowth of thyroid epithelial elements or to increase in size and contents of the acini formed by them. The ill-effects of such enlargement may be merely unsightly, causing a swelling in the neck, or mechanical, such as pressure on the trachea. Goitres of this type are usually referred to as **simple,** in contra-distinction to those which produce effects of excessive thyroid activity—hyperthyroidism—which are called **toxic.** When the hyperplasia is due to malignant disease of the gland, the goitre is said to be **malignant**—this will be referred to later under tumours of the thyroid (p. 836).

Goitres may thus be classified clinically, that is, functionally, into the above simple and toxic forms, to which may be added a third, viz., those associated with **hypo**thyroidism (myxœdema); or anatomically according to the structural changes that are found in the thyroid.

Often it is not possible to say from the structural appearances alone what the functional effects have been. For an accurate and complete opinion on any specimen of goitre, the following data are necessary, but rarely obtainable: the total size of the goitre, samples from different areas of it, its iodine-content and the basal metabolic rate of the patient. Frequently an approximate opinion is possible from the gross specimen and several histological samples of it.

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[1] The word "struma" was used originally by the old Latin writers to signify any glandular enlargement, especially in the neck, most commonly "scrofulous" or tuberculous in nature, and often known as "the king's-evil," to be healed by the touch of the king. Then the word "struma" came to be applied to an enlargement of the thyroid gland and practically synonymous with the term "goitre." The latter word is derived, through the French "*goître*," from the Latin, "*guttur*," the throat.

Goitre is also divided into the **endemic** and the **sporadic** forms. Anatomically these may be similar, but the endemic occurs in a large proportion of the inhabitants of certain districts, the sporadic has no such association.

The term " parenchymatous " [1] is often applied to a goitre where the main constituents of the enlargement are the cells of the acini rather than the content ; where the latter is in excess, the term " colloid " is applied. It seems to us that it is more satisfactory to use the terms " active," " hyperplastic " or " secretory," instead of " parenchymatous," where the main feature is the cellular activity in contra-distinction to " colloid," " passive " or " resting," where the main feature is a filling-out of the acini with a store of colloid-content.

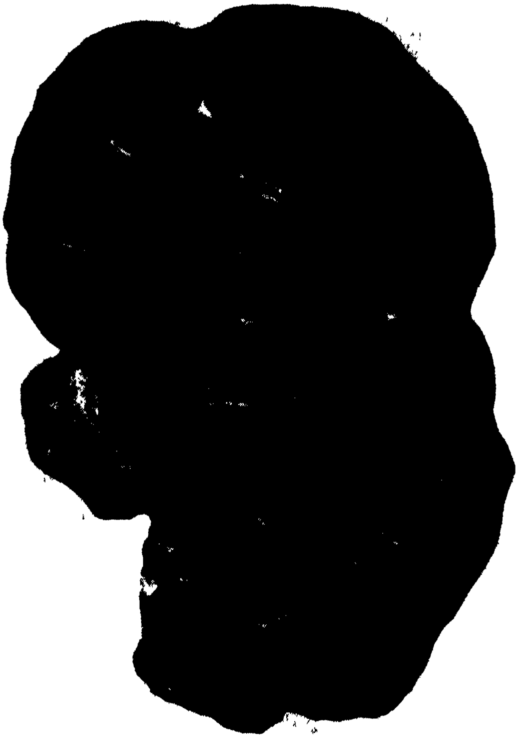

FIG. 476. *Diffuse colloid goitre.* The specimen consists of one lobe of thyroid only, and is composed of large colloid acini.

It is convenient to describe first certain types of goitre that may be found, and the secondary changes in them, before discussing the ætiology of goitre. The first type is :—

Simple Goitre. This may take the form of a diffuse enlargement of the thyroid, due, in its fully developed state, to an increase in the number and size of the acini and a filling-out of them with colloid-content—a **diffuse colloid goitre** (Fig. 476). Both lateral lobes and isthmus are enlarged and smooth on the external surface, or but slightly undulating. The cut surface has a glistening semi-translucent amber appearance and is moderately firm.

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[1] " Parenchymatous " : *see* second footnote on p. 1010.

Examination with a hand-lens will reveal the colloid-filled acini; some may even be so distended as to be recognisable macroscopically. On microscopical examination, the epithelium is seen to be low cubical or flattened, the content of the acini a uniform colloid, varying in density in different specimens. Examination of different areas may reveal amongst these inactive spaces the presence of occasional acini, single or in groups, and varying in size and shape, with a more active type of epithelium consisting of tall columnar cells; or, again, these may line the whole acinus or merely one side of it and may perhaps form little projections into it (Fig. 477). Such areas consist of spaces formed by epithelium which is either in process of reverting, or " involuting " to the resting (colloid) phase, or where a previous resting epithelium is becoming active (hyperplastic), the process being a " reversible " one.

FIG 477. *A portion of an old-standing goitre.* To illustrate appearances described in the text. Note the variation in size and shape of acini and the change in character of the epithelium of the large irregular acinus. In the colloid of the latter are many phagocytic cells filled with blood-debris from a previous hæmorrhage into this acinus. × 100.

The size of a diffuse colloid goitre of this type varies greatly. It may be but little larger than a normal thyroid or it may be huge, and weigh a kilogramme or more.

It is obvious that, at least in the larger examples, there must have been a stage of previous hyperplasia of the epithelium which has later reverted to the colloid phase—the occasional acini with the active epithelium indicating what has already taken place elsewhere. Marine has expressed this by saying that goitre is essentially a condition of present or previous hyperplasia of the special gland-tissue of the thyroid.

This type of goitre is a common form in endemic areas, but can occur sporadically. It is found in young as well as in older patients. The iodine-content per unit of substance is low—provided no iodine has been administered to the patient.

The goitre may regress and become smaller and firm; or it may continue to enlarge till pressure-symptoms demand its removal. It frequently exhibits the secondary changes (p. 830) so commonly seen in goitres of long standing and eventually assumes a nodular form. It may become "toxic" either from increase of iodine in its colloid, or from development of hyperplastic nodules.

Simple Nodular Colloid Goitre (Fig. 478). This is but a variant of the above, and, as noted, may be a later phase of the diffuse colloid goitre produced by degenerative and fibrotic changes in some parts, alternating in others with hyperplasia, reverting to colloid. Usually, in such an older goitre, there are to be found areas of activity—hyperplastic nodules—as well as those showing colloid. The iodine-content is often very low even in the colloid areas. Such a goitre can later become toxic (*see* nodular form of toxic goitre, p. 829).

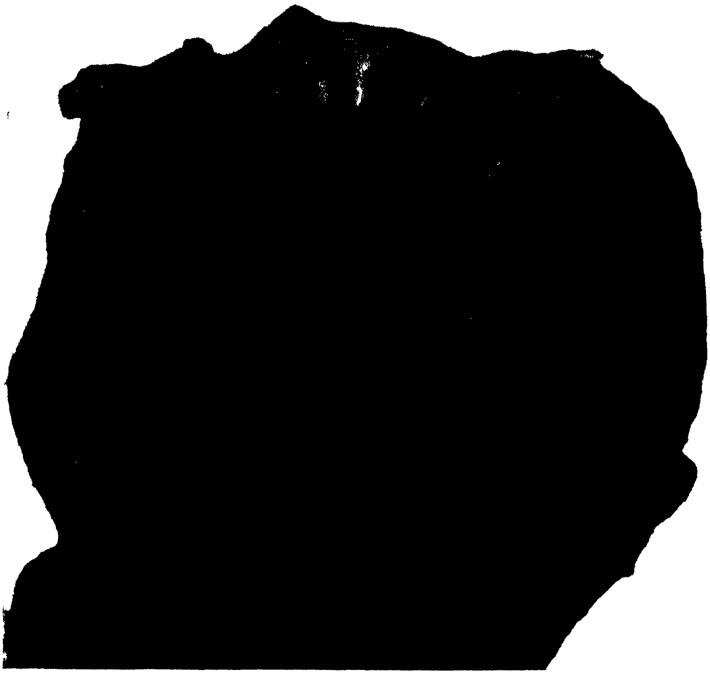

FIG. 478. *Large nodular cystic colloid goitre.*

Simple Hyperplastic Goitre. A diffuse form of this variety of goitre occurs in infants and children in certain definitely endemic areas (p. 832). The thyroid is uniformly enlarged owing to hyperplasia of its acinar epithelium, the acini are small and may be solid, the acinar content being relatively scanty and even absent. The iodine-content is very low and this goitre may be associated with hypothyroidism in the form of cretinism (pp. 833–4) or myxœdema (pp. 833–6). As the child grows, this form of goitre, in parts at least, tends to change to the colloid phase, and may thus develop into a colloid goitre with hyperplastic areas.

Toxic Goitre and Thyrotoxicosis. Under this heading are included all those goitres associated with any form of hyperthyroidism. **Exophthalmic goitre** is a variety of toxic goitre where the exophthalmos is a prominent feature; it may be "primary" or "secondary," and these varieties can be related to different pathological changes in the structure of the gland. In all forms of thyrotoxicosis the basal metabolic rate is raised.

A diffuse colloid goitre may give rise to toxicity if its iodine-content is sufficiently high, and a previously non-toxic colloid goitre may be changed to one of toxic type by excessive administration of iodine. Usually the "**primary**" **toxic goitre,** or "primary" exophthalmic goitre is of a **diffuse hyperplastic type.** The gland is uniformly but often only slightly enlarged, and the amount of enlargement gives no measure of the toxicity (Fig. 479). It is of fleshy consistence and rather like raw meat on section; as pointed out many years ago by the late Professor W. S. Greenfield, it may resemble actively-secreting salivary gland, the rapid production of secretion leading to a mucinoid rather than to the more usual colloid content of its acini. Histologically, in a case untreated with iodine (Fig. 480), the epithelium is of tall columnar type often forming papilliform projections into the acini, the lumen of which may be diminished in size and may be devoid of colloid-content, or have but a scanty mucoid content. The blood-vessels are engorged from active hyperæmia. In a case that has had iodine administered (Fig. 481), the appearances are much altered, and may even come to resemble those of a colloid goitre owing to filling-out of the acinar space and a return of the epithelium to a more resting phase. Associated with this histological change, there is an increase in the iodine-content of the gland and a lowering of the metabolic rate, though not as a rule down to normal level. The administration of iodine thus steadies the gland and induces an involution from the active (secretory or hyperplastic) phase to the passive (storage or colloid) phase.

FIG. 479. *Exophthalmic goitre.* The thyroid is only slightly but uniformly enlarged. The thymus is large and fleshy.

The subsequent history of the primary thyrotoxic goitre varies. In the milder cases, the gland may regain the colloid state and the toxicity cease. If not treated, it may remain for some years in much the same phase, though secondary

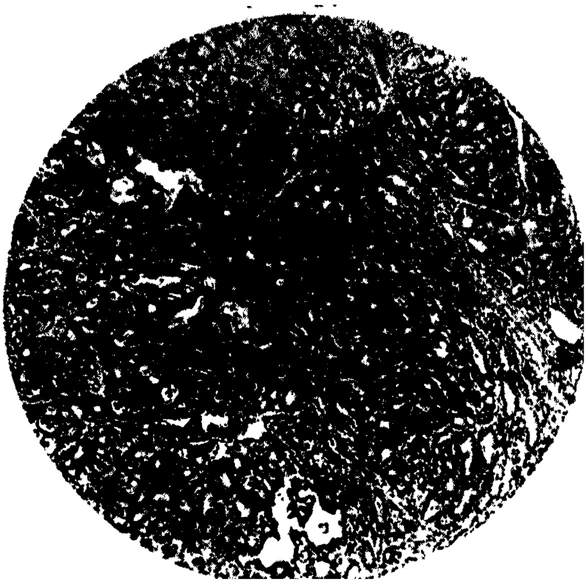

FIG. 480. *Exophthalmic goitre.* Appearance of thyroid of a case untreated with iodine. The acini are lined by columnar epithelium and the majority are small, with no colloid content. Papillary projections into the lumen can be seen, especially in a few larger acini. × 50.

changes (p. 830) are liable to occur (Fig. 484), or death from exhaustion may result, the patient being " burnt out " by the excessive activity of the thyroid. Anæmia, sometimes associated with profound changes in the bone-marrow, may occur. Exhaustion of the over-active thyroid tissue, resulting in the development of myxœdema, may supervene.

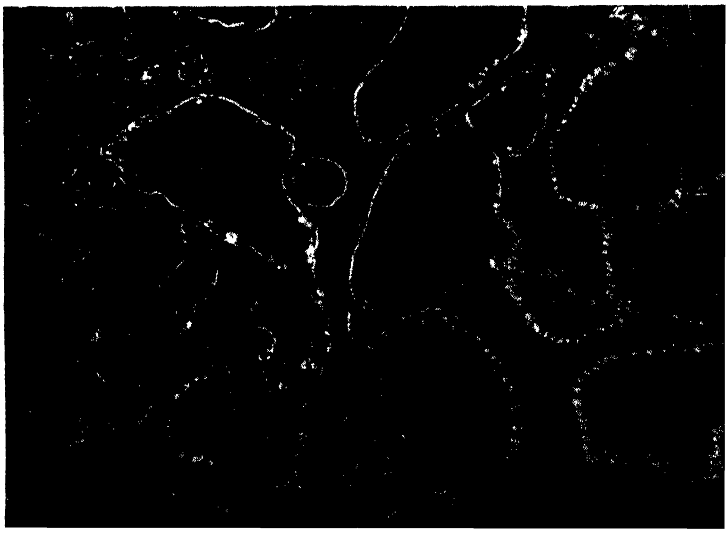

FIG. 481. Section from a primary toxic goitre. The patient was a female, aged twenty-two, to whom iodine had been administered for some time before removal of the goitre. The acini are filled with thin colloid, but lined by cubical to columnar epithelium. × 100.

Primary toxic goitre is common in the earlier age-periods and much commoner in females than in males.

Enlargement of the thymus is a not infrequent accompaniment of exophthalmic goitre.

Secondary toxic goitre is usually a nodular goitre anatomically, and is most frequently a later development in a previously simple goitre. It is much commoner in the female than in the male, and is a disease of middle life, though examples occur in either youth or old age. The usual history is one of the presence of a goitre for many years, with the recent development of thyrotoxic symptoms and occasionally exophthalmos (" secondary " exophthalmic goitre). The term " toxic adenoma " or " toxic adenomatosis " is sometimes applied to the condition, but this suggests that tumour-growth is the basis of it, and is therefore misleading (*see* p. 836).

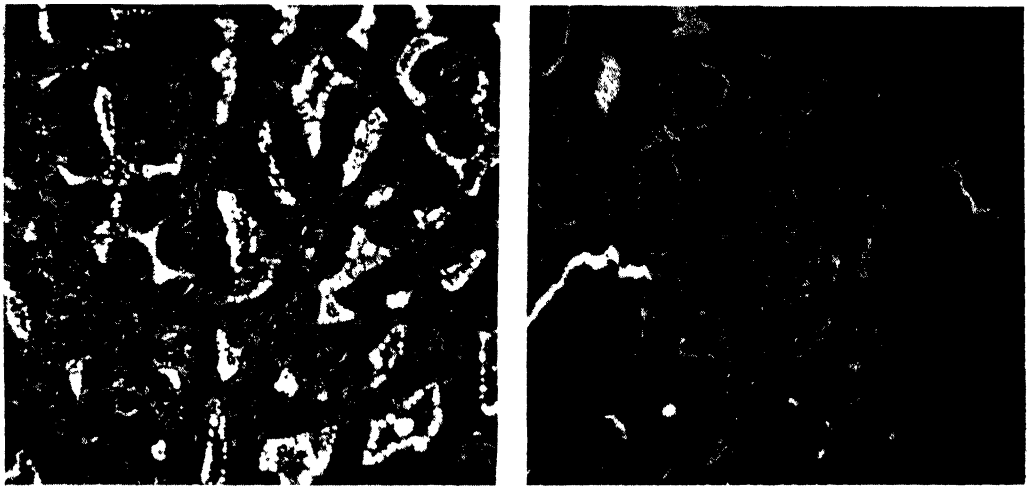

FIG. 482. *Toxic goitre :* (A) A typical hyperplastic form of goitre—acini with columnar epithelium and scanty thin colloid. Section from portion first removed. Compare with (B) for subsequent changes in the same gland. × 85.

Toxic goitre : (B) Section from second removal seven years later because of recurrence of toxicity and hypertrophy. *On right :* small atrophying acini with considerable lymphoid infiltration. *On left :* nodule of hyperplastic thyroid—several acini contain colloid. × 85.

Toxic goitre. Two specimens removed from the same patient with an interval of seven years between.

As the thyroid condition may have been present for many years, a very complicated morbid picture is often presented owing to secondary changes, and no two goitres are alike. However, certain basic changes can be elucidated as the result of study of many different specimens. In a typical example, the thyroid is enlarged and is very irregular in shape owing to its being composed of nodules of all sizes. Sometimes one lobe is much more affected than the other, occasionally the isthmus is especially altered. The nodules are bounded by displaced and compressed atrophic thyroid tissue, often accompanied by fibrous bands. On section, the goitre exhibits the same nodularity. The nodules may be composed of cystic colloid spaces or of solid fleshy hyperplastic tissue ; frequently both are present and even the same nodule may be partly colloid, partly hyperplastic. Hæmorrhages, degenerations and cysts, as secondary changes, are very common. Histologically, the hyperplastic areas may consist of small acini with high epithelium and little content, or of solid epithelial cords, which, from their resemblance to the thyroid tissue in the fœtus, are often referred to as "fœtal adenomas."

All varieties of change, from colloid acini of normal appearance to large irregular acini with partly columnar and partly low cubical to flat epithelium, are seen. At the margins of the nodules, whether colloid or hyperplastic, there are often flattened atrophic acini, some with no content, some with dense colloid.

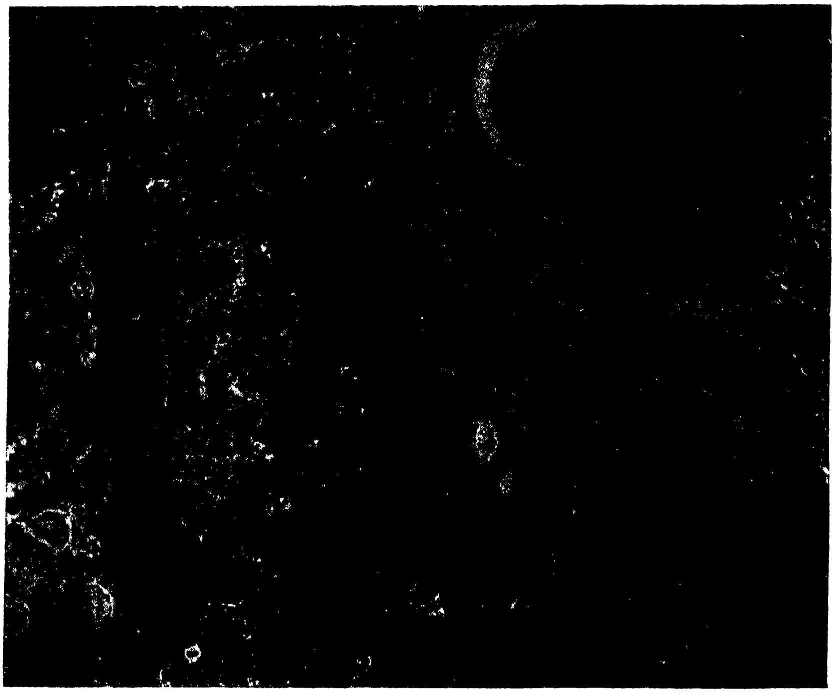

FIG. 483. *Lymphadenoid goitre.* The thyroid acini are all in various stages of atrophy and are being infiltrated and replaced by lymphoid tissue, which shows development of germinal centres. × 100.

The iodine-content varies. In the colloid areas, it may be within normal limits, or even high ; in the hyperplastic areas, it is very low. The administration of iodine may increase the iodine-content of the colloid parts, but in the hyperplastic areas it still remains low.

Hyperthyroidism or **thyrotoxicosis** is seen in the primary and secondary toxic goitres. The basal metabolic rate is raised, often markedly so. There is emaciation, tachycardia and various nervous disturbances. As the condition progresses, there may be myocardial failure from damage to the cardiac muscle, ending in interstitial fibrosis.

Secondary Changes in Goitres. Some of these have been indicated when dealing with the different types. Thus, in the later stages of a primary hyperplastic toxic (primary exophthalmic) goitre, there may be degeneration and general atrophy of the epithelium as a result of exhaustion. In some cases, the degeneration and atrophy are focal, and, around and obscuring the degenerating acini, collections of lymphocytes appear, sometimes even forming lymph-nodes. These may show to the naked eye as pale grey patches on the cut surface. The name "**lymphadenoid goitre**" (Fig. 483) has been applied to this type of change which is best regarded as a regression rather than as a special type of goitre. Some examples of Riedel's Struma (p. 823) may represent a final stage of this regression.

FIG. 484. *Nodular goitre with secondary changes.* There is much fibrosis both in and between the lobules with white patches of calcification in several, also dark areas of hæmorrhage.

Cystic changes are common. They may be produced by distension of colloid acini, or by adjacent acini coalescing, to form a large thin-walled cavity filled with colloid. Cysts may also be formed by the disintegration of a degenerated area or an old hæmorrhage; these cysts often contain cholesterol, with or without remains of blood-pigment, and are usually bounded by dense fibrous tissue.

Hæmorrhage is a common feature in old goitres, either into cystic spaces (Fig. 484, above : and Fig. 477, p. 825), or into the interstitial tissue. The hæmorrhage may be seen in its recent state as a mass of red corpuscles; but later it may be represented merely by deposits of cholesterol and pigment.

Organisation, with the formation of a dense mass of fibrous tissue, is another end-result. Fibrosis may arise in the manner just indicated, or it may supervene as a replacement-fibrosis where acini are undergoing atrophy ; and a frequent phenomenon is the occurrence of a large area of hyaline or " myxomatous " fibrous stroma in which are scattered a few acini with attenuated cells and little or no content. Lymphocytic infiltration occurs frequently in such areas. Calcification is not uncommon in any degenerating part and at times large hard masses are present ; even true bone-formation may be found occasionally. The blood-vessels of an old goitre are often sclerosed. The picture presented by an old-standing goitre is thus, as already explained, frequently one of great complexity owing largely to the presence of all varieties and degrees of the above changes (Fig. 477, p. 825).

Ætiology of Goitre :—

Many hypotheses have been advanced to account for the changes in the thyroid seen in goitre, and it is impossible here to do more than outline briefly the more important of these. For fuller details, the references already given should be consulted, and in them further references to the literature will be found.

Infections of various kinds have been claimed as causes, and, indeed, in some cases the extra demands put on the body by an infection and the damage to the thyroid epithelium may be the starting-point of a goitrous change, more especially of the primary toxic variety.

Deficiency or excess of various salts or food-substances has been advanced as likely to be causal. The influence of iodine particularly has been studied, especially by Marine and his co-workers, and by Hercus and others.

It has to be remembered that the thyroid only is capable of manufacturing its special hormone and this it can do only if the necessary small amount of iodine is supplied for its use. But the thyroid is under the general control of the pituitary and the required stimulus may come from that gland. Experimentally in guineapigs and rabbits, it has been possible to produce a toxic hyperplastic type of goitre by injections of anterior lobe of the pituitary. Even exophthalmos has been produced, but this is a pituitary-sympathetic effect, as it can occur in the thyroidectomised animal.

It has been shown that, **in endemic areas,** the **iodine-intake is low** and, because of this deficiency, the majority of the inhabitants may suffer from goitre, either diffuse or nodular in type. The iodine- or hormone- content of such goitre is often very low per unit-volume of gland, and prevention of goitre or even regression of some of the smaller goitres has been attained by administration of small amounts of iodine. Such endemic areas may be either in river-valleys, as in parts of Switzerland, or in plains, as around the Great Lakes district of America. Hercus and his collaborators have shown that, in certain endemic areas in New Zealand, the iodine-content of the soil is very low, and this is reflected in a correspondingly low content of it in the foodstuffs grown on such soil ; further, the incidence of goitre is in inverse ratio to the iodine-content of the soil.

In certain districts in which goitre and cretinism are common, the presence of **fluorine** has also been noted in the drinking-water and in the *geological strata from which it is derived, and its influence of this substance upon the thyroid gland and upon the metabolism of iodine, as well as on the incidence* of " dental fluorosis," *calls for further investigation.*

McCarrison and others have produced goitre experimentally in animals by giving various **faulty diets,** *particularly if* **deficient in vitamin-content intake,** and the giving of iodine has *not always prevented such goitre. It is reasonable* to assume that, in such instances, *the thyroid has not been able to utilise the* iodine available. It has been observed *in rabbits that a high incidence of* goitre may coincide with the excessive use of cabbage in their diet.

Many objections have been raised to the iodine-deficiency hypothesis, but that it is a factor in the production of at least endemic goitre seems fairly certain. Its application as the explanation of sporadic cases is more difficult, and in these the pituitary may be the defective link, either by inhibiting the efficient function of the thyroid or by stimulating it unduly—as is seen in the experimental production of goitre by the injection of pituitary extract mentioned above.

Whether the iodine-deficiency is in the form of low intake as in endemic areas, or deficient absorption from faulty diet, or is a relative deficiency owing to excessive demand on thyroid action with a minimal intake, the mode in which it acts would seem to be that the thyroid endeavours to counteract the deficiency by increasing its store at a lowered concentration—the diffuse colloid simple goitre of low iodine-content : or by increasing its active secretory tissue at the expense of storage—the hyperplastic goitre, diffuse or nodular. In either case, the goitre is of the nature of a compensatory reaction, and a balance is reached. But if, later, that balance is again upset by a reduction in demand for thyroid activity, or by an increased intake of iodine, the goitrous thyroid is too large for its owner, and hyperthyroidism or thyrotoxicosis develops. This is the common sequence in nodular toxic goitre, and the balance can be restored only by reduction of the excessive thyroid tissue, either by surgical means or X-ray treatment

Where the stimulus originates in the pituitary, as is probable in the primary toxic hyperplastic goitre, surgical removal of the excess of active thyroid gland balances the supply of, and demand for, its hormone, but does not directly touch the basic cause.

Functional Disturbances from Thyroid Derangements. As indicated above, these may be the result of decrease, increase, or perhaps in some instances alteration in the quality, of the secretior of the gland ; and reference has already been made to certain of the results of these, more particularly those due to increased secretion.

The consequences of diminution, like those of increase, may be of very varying degree, and may range from minor degrees of thyroid insufficiency up to those of complete athyrea. These can be discussed under three headings :

(1) **Congenital Athyrea** or **Cretinism** which may be either **Sporadic** or **Endemic** :
(2) **Operative Athyrea** brought about by total or partial **Removal** of the gland, therapeutic in the human subject, experimental in animals : and
(3) **Degenerative Athyrea** or **Myxœdema** proper.

The ultimate causation of **sporadic cretinism** with absence or early atrophy and perhaps complete disappearance of the thyroid, is not yet understood, but, unlike that of the endemic variety, it appears to have no connection with the physical characters of the soil or water-supply of the district in which the case happens to occur; nor does heredity or family-predisposition—although occasionally recorded—seem to play any constant or important part in its production. Dr. John Thomson, of Edinburgh, investigated the family-history of a considerable number of cases, and found no particular tendency to thyroid disorders among the mothers of his cretin patients, nor any history of obvious ill-health during their pregnancies.

In **congenital cretinism,** the thyroid is similarly either entirely absent, or undergoes early and perhaps complete atrophy. The body-tissues of the infant are, therefore, deprived of the influence of its secretion during the period of life at which their growth should be most active. As a result, the cretin is stunted both in body and mind, the mental condition [1] varying from facile weakness or imbecility up to complete idiocy, often combined with deaf-mutism. The basal metabolic rate is very low. The central nervous system, bones, connective tissues and skin are especially affected. The head is large, the tongue often protruding, the limbs stunted and thick-set and the hands short, broad, and with baggy wrinkled skin, and the abdomen prominent and frequently showing an umbilical hernia. The skin is lax, dry and harsh, the hair scanty : pads of redundant subcutaneous fat are usually present, especially above the clavicles : and dentition is delayed and imperfect. The infant is supplied *in utero* with thyroid hormone by the mother, and the stigmata of the disorder may thus not become apparent until several months after birth. From a therapeutic point of view it is therefore important that the diagnosis should be made as soon as possible, as comparatively normal health may be maintained if thyroid medication is instituted sufficiently early. Cretins are specially liable to be attacked by infective diseases such as general tuberculosis, tuberculous and other forms of meningitis, or pneumonia ; and the symptoms of these are often masked to an extraordinary extent, evidence of their unsuspected presence being sometimes discovered only on post-mortem examination.

Endemic cretinism is found in districts in which goitre is also prevalent, the causes of which are discussed on pp. 832–3. **Two forms** of endemic cretinism are described : the **myxœdematous** in which the parathyroids survive—the commonest type found in Europe : and the **nervous**, in which these glands (*cf*. pp. 837–8) are involved along with the thyroid. Both of these types were described by McCarrison as occurring in the " endemic valley-regions " of the North-West Provinces of India, his cases often combining the clinical features of both, and **deaf-mutism** being a common accompaniment of either variety.

Operative athyrea or an acute form of **myxœdema following upon thyroidectomy.** Unless the secretion of the thyroid has already become diminished or much modified by disease, and if thyroid medication is not immediately instituted, the complete removal of the gland is followed by very acute symptoms, though the intensity of these depends to some extent upon the species of animal employed, and also upon its age, young animals being most susceptible—and the results being more serious if the parathyroids are also removed. Full descriptions of such experiments on animals are to be found in textbooks of physiology : and the results of thyroidectomy, total or partial, for disease in the human subject, are given in textbooks of surgery.

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[1] In this connection, the origin of the word " cretin " is of interest. In Chambers's English Dictionary it is given as " Fr. *crétin*—Swiss *crestin*—L. *christian-us*, probably implying that, after all, they are human, or that they are (from their fatuousness) incapable of sin, and therefore viewed with some degree of religious respect—*cf.* the frequent use of *innocent*."

Degenerative Hypothyroidism, Athyrea, or **Myxœdema proper.** Although acute forms of this disorder occasionally occur, it is much more commonly chronic and due to the presence of slowly progressive degenerative and atrophic changes, by which the gland is gradually converted into a mere mass of fibrous tissue, with disappearance of its glandular structure (Fig. 485). In its earlier stages, invasion of the stroma with numerous " small round cells " takes place, and the gland comes to have a structure resembling that of lymphadenoid tissue (*cf.* pp. 823 and 830–1, and Fig. 483, p. 830). These changes may come on insidiously, with no as yet ascertainable cause ; but, in some instances, they follow certain other lesions such as toxic goitre (pp. 827–30), the degenerative process supervening upon previous increased activity and enlargement. Patients so affected therefore may present a symptom-complex which partakes in varying degree of both conditions. Like thyrotoxicosis, myxœdema occurs much more frequently in women than in men, the relative proportions in myxœdema being given by Osler as about 6 : 1. An increased liability to disease of the thyroid has in some instances been noted in members of the same family, and numerous instances in which both myxœdema and thyrotoxicosis (*e.g.*, in the form of " exophthalmic goitre ") have occurred, *e.g.*, in sisters, are recorded. The condition of some patients suffering from congenital cretinism may, as they grow up, gradually change and come to resemble one of myxœdema. In certain rare instances, following perhaps upon an attack

FIG. 485. Atrophic fibrosed thyroid, from case of myxœdema. The acini are small, the cells of many being atrophic and colloid is lacking. There is excess of fibrous tissue. × 100.

of some acute infective disease, a myxœdematous state develops in older children, the condition being then known as **juvenile myxœdema.** Myxœdema, however, attacks mostly middle-aged women. The patient develops a heavy sluggish appearance ; physical and mental processes are slowed down, and the metabolic rate much lowered. The temperature is subnormal ; there is increased tolerance for sugar ; circulatory and respiratory activities are lessened ; and the sexual functions are diminished or in abeyance. There is atrophy of the sebaceous and sweat-glands and hair-follicles, and, as a result, the hair falls out. Excess of " gelatinous " or " mucinoid " material appears in the subcutaneous tissues, giving a puffy appearance to the face and participating in the formation of the so-called " supraclavicular pads." Similar " mucinoid " accumulation may be found in the connective tissue of peripheral nerves (Fig. 760, p. 1186), and degenerative changes be present in the nerve-fibres and cells of the central nervous system. The bone-marrow also tends to undergo mucinoid degeneration (p. 608), associated with the development of a progressive anæmia. The complexion has a yellowish tint, and there is often a peculiar localised pinkish malar flush. Myxœdematous patients, like cretins, are very liable to be attacked by infective disease, especially tuberculosis, and, as pointed out by the late Professor Greenfield, who was one of the pioneers in the investigation of the myxœdematous state, the tuberculous infection may run a rapid and " latent " course, *i.e.*, give rise to little or no clinical evidence of its presence. Thyroid medication can, if not unduly delayed, restore the patient's health practically to normal, and in appropriate dosage may maintain it so even into old age.

TUMOURS. The occurrence of simple **adenoma**, usually in the form of a rounded, well-defined tumour in an otherwise healthy thyroid, is not infrequent. Histologically, it may be of either hyperplastic or of colloid type. It may be functionally active, causing a thyrotoxicosis, and in that sense is a true " toxic adenoma." As discussed under thyrotoxicosis, the so-called " toxic adenoma " of goitre is of the nature of a compensatory hyperplasia (p. 829).

Carcinoma occurs as a primary growth. It may be of spheroidal-celled type (carcinoma simplex), but more commonly it is in the form of an adeno-carcinoma of small acini sometimes devoid of lumen or content ; occasionally it resembles more closely ordinary colloid thyroid. Papilliferous cystic carcinomas are found occasionally in the thyroid, but are of commoner occurrence in accessory thyroids than in the main gland itself. They originate possibly from post-branchial (ultimo-branchial) bodies. Thyroid carcinomas are commoner in goitrous than in normal glands ; they tend to invade the thyroid veins (Fig. 486)[1] and the trachea may be infiltrated. **Sarcoma** is a rare tumour. Occasionally, anaplastic carcinomas simulate sarcomatous growths, but true sarcoma of spindle- or round-celled types may occur. Metastases from tumours elsewhere may be found in the thyroid.

Parasites. Hydatid-cysts can occur in the thyroid, but are rare even in geographical areas in which hydatids are common. **Trypanosoma cruzi,** which occurs in Brazil, is found to be associated with a form of thyroiditis known as Chagas' disease (p. 370).

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[1] This Fig. 486 will be found in the Appendix, p. 1258, at the end of the book.

DISEASES OF THE PARATHYROID GLANDS[1]

The parathyroids are usually four in number in man, two on each side, situated laterally outside the thyroid capsule, though one or more may be embedded in the thyroid substance. There may be less or more than four. When less, the remaining glands may be larger than the normal average size which is about that of a lentil[2] (approximately 6×4×2 mm.). They are oblong and of a yellowish-brown colour and often difficult to find. Aberrant parathyroids may occur in the thymus, along the carotids and even in the connective tissue of the mediastinum. Embryologically, they arise from the third or fourth branchial pouches, that is, from the same source as that from which the thymus is derived.

In structure, they possess a fibrous capsule and a rich sinusoidal capillary meshwork between their parenchymatous cells. These are of two main types, the " principal " or " chief " cell and the " oxyphil " cell. The former is in much greater numbers than the latter and has either a clear, poorly-staining cytoplasm (the " clear " principal cell) or a more deeply-staining cytoplasm (the " dark " principal cell) ; both forms have a small vesicular nucleus. The oxyphil cell is larger, with cytoplasm which stains readily with eosin and similar acid dyes, hence its name. There seems to be no regular arrangement of these various cells ; and their proportions vary in different glands and at different ages. It is not known whether the two types have separate functions, or which produces the specific hormone, " parathormone," which controls the calcium-phosphorus metabolism and the balance of these substances in blood and tissues, especially bone.

Extirpation of the Parathyroids, either in man or animals, leads to **tetany.** This may be acute, as in experimental removal or accidental removal during a thyroidectomy. Muscular spasm and tremors ensue, exaggerated reflexes, dyspnœa, tachycardia and a raised temperature. If not treated by injection of hormone, death follows in a few days or weeks. The presence of aberrant or ectopic parathyroids may prevent the occurrence of these symptoms or may permit them only in much less severe form.

The symptoms of tetany are due to **loss of blood-calcium,** as this element decreases the excitability of nerve. The normal blood-calcium is 9 to 11·4 mgr. per 100 c.cm. of blood and when the parathyroids are removed or are not functioning, calcium cannot be utilised and the blood-calcium falls. When this diminution reaches about 7 mgr. per 100 c.cm., symptoms of tetany begin to appear.

Tetany can occur quite apart from removal of, or damage to, the parathyroids, as in rickets (p. 1214 and *cf.* p. 1218) : or other circumstances may reduce the available calcium, such as excessive vomiting which leads to the production of alkalosis—a frequent cause of tetany in children. Examples of tetany occur without obvious cause and are then termed " idiopathic."

Excess of parathyroid activity may arise from hyperplasia of the glands from as yet unknown causes, or from tumour-growth of the nature of an adenoma, the cell-type of which is usually the " principal " cell ; the general structure of the adenoma closely resembles that of the normal parathyroid. Usually only one gland is involved, but two or more may be adenomatous. The usual result of the excess of parathyroid tissue is hyper-parathyroidism, though adenomas of the gland have been recorded in which this condition was absent.

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[1] For fuller details see the review by D. L. Thomson and J. B. Collip " The Parathyroid Glands," *Physiol. Rev.*, 1932, **12**, 309, or A. Crotti, " Thyroids, Parathyroids and Thymus," 1938, 3rd ed., Henry Kimpton, London.

[2] See footnote on p. 1038.

Hyperparathyroidism causes an excessive mobilisation of calcium and an increase of blood-calcium to 15 mgr. or even more per 100 c.cm. The blood-phosphorus is usually lowered from the normal range (2·5 to 4 mgr.) to 1 mgr. or even less. There is an excessive excretion of both calcium and phosphorus in the urine. Even if the blood-calcium findings are normal or but little raised, studies of metabolism show a "negative calcium" and "negative phosphorus" balance, that is, more is being excreted than is ingested. The deficit comes from the stores of calcium and phosphorus in the bones; consequently there is a generalised decalcification of all the bones, leading to the production of the condition of **generalised osteitis fibrosa et cystica,** the details of the bone-changes of which are given elsewhere (pp. 239–241 and 1211). In addition to osteitis fibrosa, other pathological conditions may be found—for example, the excess calcium may be deposited in the kidney, producing a nephritis, or more commonly a pyelonephritis with calculus-formation : also in the walls of many blood-vessels, and even in the muscle-cells of the heart and of the stomach. This scattered deposition of calcium is usually called "**metastatic calcification**" and a similar result may follow excessive overdosage with vitamin D. Indeed, many of the effects of hyperparathyroidism can be reproduced by hypervitaminosis D (p. 441).

Fig. 487. *Adenoma of Parathyroid.*

Phosphatase, which is the enzyme concerned with the splitting of organic phosphates, and found especially in ossifying cartilage, is increased in amount in the blood ; but this increase may be secondary to the osteitis, as it is found also in rickets and Paget's disease of bone, in which no hyperparathyroidism has been demonstrated. Minor grades of parathyroid hyperplasia are described as occurring in rickets and osteomalacia.

Experimentally, as demonstrated by Collip, it has been found possible to produce in animals changes similar to those occurring naturally in man by giving the parathyroid hormone. In man, removal of the excess of parathyroid tissue, or adenoma, leads to a restoration of calcium-phosphorus balance and cures the osteitis fibrosa (p. 1211).

The growth and activity of the parathyroid cells is, like those of the other endocrine glands, controlled by the **pituitary master-gland,** in this instance through the influence of a so-called "**parathyrotropic substance.**"

DISEASES OF THE THYMUS

The thymus still remains something of a problem as regards its function and relationships to the other endocrine glands. It is even doubtful if it should be included as a member of the group.

It arises from the same branchial pouches as the parathyroids, *i.e.*, the third and fourth, which explains the occasional occurrence of aberrant or ectopic parathyroids embedded in the thymus. Although originally an epithelial organ embryologically, it becomes invaded by mesoblastic cells of lymphocytic type and comes to consist of areas of lymphadenoid tissue, each with a peripheral zone of small-type lymphocytes and a medullary portion of large lymphoid cells supported by a reticulum, said to be of epithelial origin. In the medullary areas are the peculiar Hassall's corpuscles which are so characteristic of the organ and which may represent the surviving portions of the original epithelial outgrowths.

The organ consists of two lobes lying at the root of the neck and passing downwards behind the upper part of the sternum to overlap the pericardium anteriorly.

In spite of many experimental studies, its function remains obscure. It has been credited with having a profound influence on metabolism, especially of calcium and phosphorus, and its removal as being a cause of death in coma. On the other hand, some observers found that it was not essential to life and that its removal seemed to produce little if any untoward effects. Rowntree and others have found that an extract of thymus given intraperitoneally to rats over several generations produced, in later litters, an abnormal rate of growth and sexual precocity.

The thymus is, relative to the size of the individual, largest at birth, its average weight being then about 21 grammes. It increases in size up to puberty when its average weight is about 34 grammes, at twenty years it is about 25 grammes, and it thereafter steadily declines in weight. Its remains may still be detectable, embedded in fatty tissue and much atrophied, in old age.

Atrophy, as just stated, occurs in old age ; but it is found also in wasting diseases and in starvation.

Hypertrophy occurs in many cases of goitre, more particularly in the toxic varieties, and being, as was originally pointed out by the late W. S. Greenfield, sometimes pronounced in exophthalmic goitre (p. 827, and Fig. 479). In Addison's disease (p. 842B), in contra-distinction to the characteristic general wasting, the thymus is not infrequently found enlarged. In myasthenia gravis (p. 1245), hyperplasia of the thymus not infrequently occurs, and improvement following upon its removal or its artificial atrophy by irradiation is described.

Status Thymo-lymphaticus (*cf.* p. 686). The existence of this as a disease-entity has been seriously called in question, but the fact remains that in certain individuals a condition of large, or persistent, thymus is found, usually in association with hyperplasia of lymphoid tissue in the pharynx, intestinal lymphoid areas and in the Malpighian bodies of the spleen ; frequently also there is hypoplasia of the aorta and larger arteries. Individuals, especially children and young persons displaying such features, have long been recognised as being liable to sudden death from trivial causes, such as minor injuries, the shock of cold *water in bathing and during the induction of anæsthesia. What the relationship is between these appearances and the apparent effects remains obscure. There is, as yet, no experimental evidence to support the idea of risk of sudden death from excess of thymic secretion.*

In children, the thymus may press upon the trachea and even produce death from this cause, probably aggravated by engorgement of the gland or hæmorrhage into it. In the new-born, such hæmorrhage may be the result of delivery. Minor degrees of enlargement may produce pressure on the trachea and lead to the occurrence of reflex bronchial spasm (thymic asthma).

Infections. Small acute abscesses may occur in the thymus as part of a pyæmia ; larger pyogenic abscesses are seldom seen. Tuberculosis is rare, but miliary foci and larger caseous areas may be found. Syphilis, in the form of gummata, is also rare.

Tumours. Benign tumours are rare, but the following have been described : lipoma, myxoma, fibroma and dermoid. Malignant tumours are also uncommon, but constitute one form of mediastinal tumour. Either sarcomas and carcinomas occur, probably because of the dual nature of the gland-tissue. Sarcoma is the commoner, especially in the form of lymphosarcoma, though other cell-types have been found. Carcinoma may take the form of squamous epithelioma and Hassall's corpuscles may be found amongst the tumour-cells, possibly forming their origin ; encephaloid forms of carcinoma have been noted. Leukæmic infiltration of the gland may cause enlargement.

DISEASES OF THE SUPRARENAL, OR ADRENAL, BODIES

Development. Developmentally and physiologically, the suprarenal consists of two distinct portions, the **cortex** and the **medulla.** In man and other mammals, the medulla is completely enclosed within the cortex ; but, in amphibia, reptiles, and birds, they merely interlock ; whilst, in fishes, they remain as anatomically separate organs.

The cortex is derived from mesodermal cells lying adjacent to the genital ridge and is at first distinct from the medulla, which is developed from the ectodermal tissue which also produces neuroblasts. The medulla is of similar origin to the sympathetic ganglia, and the neuroblastic cells gradually invade the cortical tissue until they come to lie in the midst of it. These cells become differentiated from those destined to become nerve-cells by the development in them of a chromaphil (or " chromaffine " or " phæochrome ") pigment.

In the human fœtus, the suprarenals are of relatively large size, owing to the greater development of the innermost part of the cortex next the medulla. This well-developed boundary-zone does not show lipoid granules, but, after birth, the cells undergo fatty degeneration and disappear by about the end of the first year of extra-uterine life. At birth, the portion of the cortex superficial to this boundary-zone is narrow, but, *pari passu* with the atrophy of the fœtal boundary-zone, it gradually enlarges to form and constitute the adult cortex.

Structure :—

On naked-eye examination, the flattened irregularly triangular pyramidal bodies with rounded edges exhibit, **on section,** a radially striated, yellow-ochre-coloured cortex, the tint of which usually becomes darker as age advances. The medulla or central portion of the gland varies greatly in bulk, and is slightly translucent to opaque pearly-white in appearance, though in many cases it may, from the presence of pigment, present a dark-brownish tint. **On microscopical examination,** the cortex may be differentiated into three zones, the superficial **zona glomerulosa**: the narrower, radially arranged columns of the **zona fasciculata,** which constitutes the main bulk of the cortex: and the deepest layer of the cortex—the **zona reticularis.** In the human subject, these various layers run gradually into one another. The cortical cells are rich in fatty and lipoid substances, which may disappear in disease. The **medulla,** or central portion of the gland, contains numerous thin-walled, dilated venous-capillary spaces, into which the blood from the cortex directly flows. Between these spaces lies a reticular stroma, in which are embedded groups of polyhedral or irregular cells, which are clearer and more vacuolated than those of the cortex. They are arranged in irregularly-anastomosing columns, surrounding large blood-sinuses which are continuous with those of the zona reticularis. These cells contain numerous granules, especially those having a special affinity for chromic acid and its salts, by which they are stained brown or yellowish-brown, and hence termed **chromaphil** (or " chromaffine ").

The course of the blood-flow in the suprarenal somewhat resembles that of the lymph in a lymph-node, the arteries being distributed to the periphery like the afferent lymphatics, and giving rise to a rich capillary plexus running between the columns of the zona glomerulosa and zona fasciculata. In the zona reticularis, these become large and sinus-like, and, from the latter, the blood passes directly into the venous sinuses of the medulla, from which it is collected into the single vein which leaves the hilum like the efferent lymphatic.

Function. The cells of the medulla produce the internal secretion variously termed adrenaline, epinephrine, suprarenin, etc., which chemically is methylamino-ethanol-catechol. The lævorotatory form of this is the active form found naturally and prepared synthetically. It acts on the structures supplied by the sympathetic, the point of action being the neuro-muscular junction. Generally speaking, it increases blood-pressure by causing constriction of the arterioles. The effects vary according to the amount of adrenaline administered. The details concerning this hormone are given fully in works on physiology and need not be described here. Since the importance of the cortical secretion has become recognised, the medullary hormone has been relegated to a minor position and indeed it is now regarded as not essential to life.

The cortex is essential to life, the experimental removal of both suprarenals resulting in rapid death of the animal unless suitable cortical extracts be administered. Similar effects occur in man where destruction of all cortex has occurred from disease or removal.

The cortex is concerned with the control of sodium-ions, usually in the form of sodium chloride. Absence of the cortical hormone leads to an excessive loss of sodium, with an accompanying loss of water and dehydration of the tissues. Related to these effects are the following findings, present in varying degrees in Addison's disease (p. 842B), viz., concentration of plasma-protein, loss of weight (and probably also the vomiting), anorexia, muscular weakness, diminished blood-pressure, increase in non-protein nitrogen and increase of phosphate in the blood. Carbohydrate-metabolism may be disturbed, hypoglycæmia being produced. There is still some doubt as to whether the latter may not be a medullary rather than a cortical effect, the experimental findings being still somewhat contradictory.

The exact mechanism of many of the phenomena resulting from suprarenal removal, or destruction, is still obscure, but the fact remains that treatment with active extracts of cortical tissue can remove the symptoms and restore the animal or man to relative health. Even the administration of sodium chloride in sufficient amount will remove many of the symptoms, as these are due largely to its loss and the resulting dehydration.

Szent-Györgyi (1929) showed that the cortex contains large amounts of vitamin C, known variously as hexuronic, ascorbic or cevitamic acid, and recently produced synthetically (p. 442). Some animals such as the dog and rat seem to have the power to synthesise vitamin C, whereas man, monkey and guineapig are unable to do so. This may indicate a difference in functional ability of their respective suprarenals.

That the cortex has a relation to sex is also known, though the mechanism is obscure. Reference is made to this question on p. 847 and *cf.* p. 817.

In suprarenal deficiency, pigmentation may be abnormal (pp. 218–222). This has been ascribed to the fact that adrenaline is closely allied chemically to tyrosine which can form melanin-like pigments under enzyme-action. The idea that the tyrosine which would have gone to form adrenaline in the intact gland becomes transformed into extra pigment when the medulla is destroyed is probably incorrect.

Heat-production is said to be increased (Marine and Baumann, 1922) when the adrenals are removed, but thyroidectomy prevents such increase. This may be due to removal of an inhibitory mechanism acting on the thyroid *viâ* the pituitary. The sudden structural changes in the suprarenal after birth, when the fœtal type of cortex is replaced by the adult form, may be associated with the sudden need for a new heat-regulating mechanism on the part of the infant as compared with the fœtus.

DEVELOPMENTAL ABNORMALITIES. The most important of these is the occurrence of **Accessory Suprarenals,** which may consist of cortex alone, medulla alone, or a combination of both. They vary from the size of a pin's head to that of a pea or a bean and are situated most frequently in the immediate neighbourhood of the main suprarenal; but they may be found on the surface, or in the substance, of the kidney, or, more rarely, of the liver, along the abdominal aorta, and even in the broad ligament,[1] in the walls of hernial sacs (MacLennan), or in connection with the epididymis; and, in these various positions, they may give rise to tumour-formation (pp. 283, 852, and also p. 845, *et seq.*) Such aberrant suprarenals consist, as a rule, mostly of cortex, and may be recognised by their characteristic ochre-yellow colour. A varying amount of medulla may occur in the larger "rests"; whilst accessory glands consisting of medulla-like structure alone are known as **chromaphil** ("chromaffine") **bodies** or **paraganglia** (the organs of Zuckerkandl). The **Carotid Body** or **Carotid "Gland"** has been thought to be of similar nature, but is now regarded as of the nature of a "glomus" (p. 849).

Absence of the fœtal boundary zone has been noted in the anencephalous fœtus (Elliott and Armour, 1910–11), the suprarenal of which thus resembles the adult gland; the reason for this is obscure. Absence of one gland may occur.

Persistence of the boundary zone and **hypertrophy of the cortex** may be associated with sexual precocity and other abnormalities, especially pseudohermaphroditism (Fig. 488 on p. 842A, opposite), whilst castration is said to lead to cortical hypertrophy. Malposition of the entire suprarenal gland may occur in some cases, and the organ may be partially, or even entirely, embedded in the adjoining kidney. The right suprarenal may similarly be found on the surface or in the substance of the liver. In cases of displacement and malposition of the kidney, the suprarenals usually do not accompany the kidneys, but are found in their normal position.

Atrophy. Minor degrees of atrophy are common in various conditions characterised by wasting of the body-tissues generally. It is also a feature of Simmonds' disease (p. 810), where the primary cause is pituitary deficiency. An extreme degree of atrophy is the cause of some cases of Addison's disease (p. 842B), but the antecedent cause of the suprarenal atrophy in such cases is obscure. Both glands may be reduced to a few shreds of tissue very difficult to find and identify.

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[1] In the ovary, the corpora lutea, or lutein-bodies, of menstruation and pregnancy have on account of their yellow-ochre colour, not infrequently been mistaken for suprarenal "rests" and tumours. They are, of course, a normal phenomenon in the ovary, following the discharge of the ovum from its ovisac, though tumours occasionally arise from them.

Fatty Changes. Normally the cortical cells contain fats and lipoids in the form of cholesterol-esters. These are increased in pregnancy and often in chronic renal disease. They are diminished in acute infections.

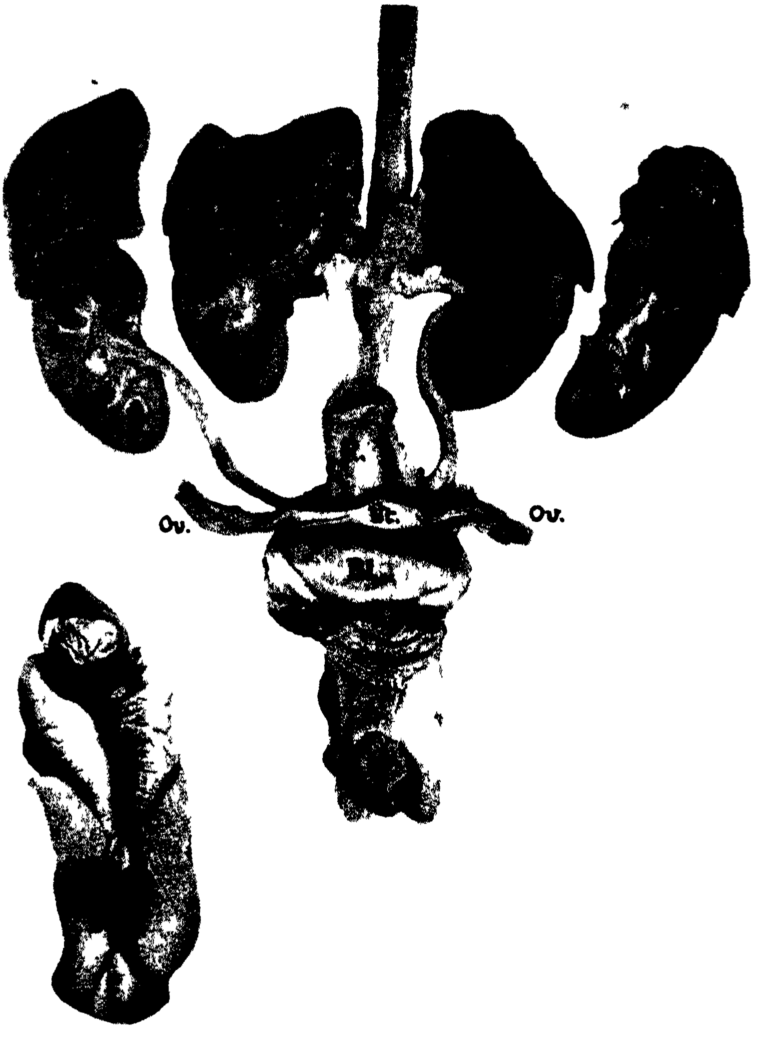

Fig 488 Greatly enlarged suprarenals from a pseudo hermaphrodite infant, aged five weeks, believed by its parents to be a male The clitoris is enlarged and simulates a penis with its prepuce (*Ut* Fundus of uterus *Ov* Ovaries *Bl* Bladder *R* Rectum) Each kidney and suprarenal is cut coronally and both halves are shown The lower left hand figure shows the perineum, from anus to clitoris (Carnegie Dickson and Sir John Fraser's case, R H S C , Edinburgh, described by Berry Hart, *Edin. Med Jour* , Oct , 1914)

Amyloid degeneration is often well seen in these glands It occurs from the usual causes, and shows the ordinary method of distribution of the disease, *i e* , in the connective tissue of the small arteries, etc. (p 208 *et seq*)

Pigmentary changes are common, especially in old persons, the colour of both cortex and medulla becoming much darker, apparently from increase in their normal pigment (p. 222).

Acute Changes. There may be the usual changes of cloudy swelling in acute infections; and focal necroses are not uncommon. Abscesses are comparatively rare in the suprarenals, but, when present, may attain a considerable size.

Acute hyperæmia of the glands—especially of their medullary portions, which may become much softened—occurs in acute infective diseases, in which **hæmorrhages** are also not uncommon, especially in scarlet fever, diphtheria, and cerebrospinal fever, and in some so-called "blood-diseases" characterised by bleeding. Such hæmorrhage may be severe, causing destruction especially of the medulla and producing a distension of the gland resembling a blood-cyst. These hæmorrhages are sometimes bilateral, and have been described as occurring in newly-born infants in whom they are a cause of sudden death (Fig. 489). Their occurrence may be due to the rapid degenerative changes in the fœtal cortex at birth favouring bleeding. Violent efforts at artificial respiration may be an immediate determining factor.

FIG. 489. *Bilateral hæmorrhage in suprarenals.* Each gland is distended by a large hæmorrhage in its interior which has destroyed the medulla and most of the cortex. From a case of sudden death in an infant.

Syphilitic changes rarely show as definite histological lesions, but these do sometimes occur, especially in congenital syphilis, in which gummatous masses are found occasionally in the suprarenals.

Tuberculosis of the suprarenals, in some of its forms, is very important. The lesions in these organs may be part of a more widespread tuberculosis, or the suprarenals alone may be affected. Small miliary tubercles are found in general tuberculosis, especially in children, and are of themselves of no special importance. In the adult, lesions varying in size from such small acute miliary up to larger caseous areas may be found. As long as these are scattered, they lead to no immediate serious results; but, when the condition becomes more advanced, as, for example, in **chronic caseous tuberculosis of the entire gland, or the greater part of it, on both sides,** it tends to produce **Addison's disease,** owing to destruction of the glandular tissue and consequent loss of the function of the gland. (Fig. 490, opposite.)

ADDISON'S DISEASE

Addison's Disease[1]—so called after Dr. Thomas Addison, of Guy's Hospital, who first described the condition in 1855—is, in the majority of cases, associated with the destruction of both suprarenal bodies, with loss of their special internal secretion. Such destruction is usually caused, as above-mentioned, by chronic caseous tuberculosis, or, more rarely, by chronic fibrous atrophy of the organs. An analogous acute condition leading to a fatal issue may be produced experimentally in animals by the complete removal of the glands. Cases in which both suprarenals have been removed, or destroyed by disease, without the production of Addisonian symptoms may possibly be accounted for by the presence of accessory suprarenals, or by the functioning of chromaphil tissue elsewhere. Minor degrees of suprarenal insufficiency can occur without the full syndrome of symptoms.

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[1] Not to be confused with "Addisonian anæmia," the term now employed to replace the older and inappropriate term "pernicious anæmia" (p. 646).

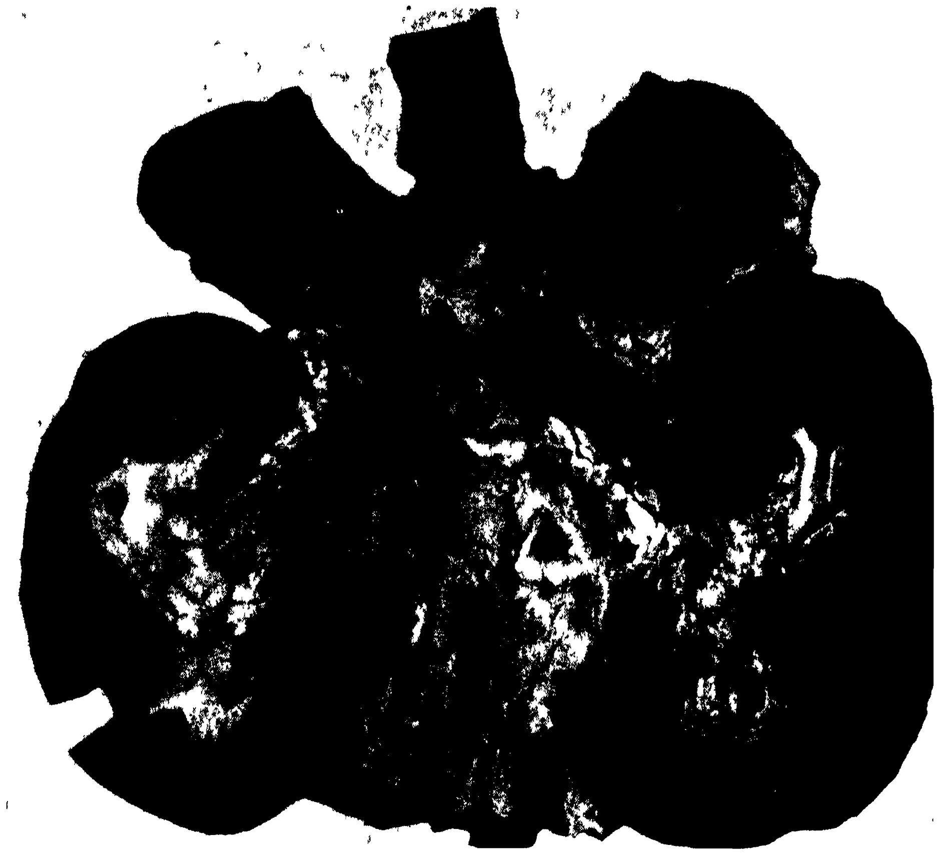

FIG. 490 *Tuberculous suprarenals—Addison's disease.* Both glands are extensively destroyed and replaced by fibro-caseous tuberculosis.

The disease occurs usually during the third and fourth decades of life—and is characterised by progressive asthenia, with great general muscular and cardiovascular weakness and lowered blood-pressure : emaciation : gastro-intestinal disturbances, such as nausea, vomiting, and diarrhœa : and by pigmentary changes in the skin, mucous membranes, and elsewhere. There is usually anæmia, though, in some of the recorded cases, there has been no great diminution in the number of the red corpuscles. The temperature is, as a rule, subnormal. Sodium-loss with dehydration, potassium- and non-protein-nitrogen retention, etc., occur, as already described in discussing the function of the cortex (p. 841).

The **colour of the skin** varies from a light brownish-yellow to a deep brownish-black. This "**bronzing**" is due to an increase of pigment in the deeper part of the rete Malpighii and in the superficial parts of the connective tissue of the corium, especially around some of the blood-vessels. It is usually diffuse, but occasionally finely-punctate, the pigment being, for the most part, contained in the cells, but also lying to some extent free in the lymph-spaces. This pigmentation is usually most marked on parts of the skin exposed to any irritation (*e.g.*, the pressure of a belt), and to the action of light, *e.g.*, the neck, face and hands. An abnormal increase is also found especially in positions where cutaneous pigment normally abounds, viz., in the axillæ, areolæ of the nipples and external genitals. Certain of the mucous membranes commonly show a patchy brownish pigmentation, especially on the tongue, the inner surface of the lips and cheeks, the gums, and other portions of the buccal mucous membrane. Patches of pigment may be found also in the conjunctivæ, vagina, and, it is said, in certain of the serous membranes. In some of the more acute cases, the bronzing of the skin may be absent.

The heart-muscle is usually soft and flabby, and may show marked brown atrophy. The spleen is sometimes enlarged and congested.

Changes in the Suprarenals :—

(*a*) **Chronic tuberculosis with caseation** is the commonest lesion, both organs being affected, though often in varying degree (Fig. 490). There is extensive destruction of the glandular tissue, the organs being enlarged and irregular in shape. The caseous nodules are often surrounded by dense fibrous tissue due to chronic proliferative inflammatory changes which tend to produce adhesions to the surrounding fat, etc. **On section,** they may be firm and fibrous, or softer and more caseous. Fibroid bands may be found among the caseated debris, and the latter may undergo calcification.

The disease is not necessarily associated with tuberculous disease elsewhere, though this is not infrequently found in other parts of the body, for example in the lungs, joints, spine or lymph-nodes ; yet, in ordinary cases of tuberculosis, there may be widespread tubercles throughout the body and perhaps none in the suprarenals. It is, therefore, difficult to explain why these two organs should, in certain cases, be specially attacked by tuberculosis, as they are far apart and small in size. It is possible, indeed, that they are rendered liable to such attack by the presence of some other previous, as yet unrecognised, primary lesion, or because they have, relatively to their size, a very abundant blood-supply with a rich capillary meshwork between their cells.

(*b*) **Chronic fibrous atrophy** may also, but more rarely, produce the disease. This change is a chronic fibrosis with extreme atrophy of the glandular structure, analogous to the changes observed in the thyroid gland in myxœdema. In such cases, it is sometimes difficult to discover the fibrous remains of the atrophied suprarenals, unless the arteries be traced to them. There is frequently considerable infiltration of the few remaining groups of suprarenal cells and the fibrous tissue by lymphocytes (Fig. 491).

(*c*) **Amyloidosis** and (*d*) destruction or replacement by **Neoplasm** are other causes of Addison's disease which are encountered much less frequently than those previously mentioned.

Acute Insufficiency. Cases of acute and often rapidly fatal illness due to sudden destruction of the suprarenals are on record, the commonest cause of this being hæmorrhage into, or thrombosis in the vessels of, both glands. An acute termination may supervene where glands, previously extensively but not completely damaged, are finally destroyed by some superadded acute lesion. In all such instances, the symptoms vary from acute abdominal pain and shock to sudden death, or death preceded by coma and resembling an apoplexy. There may be a short period of profound asthenia.

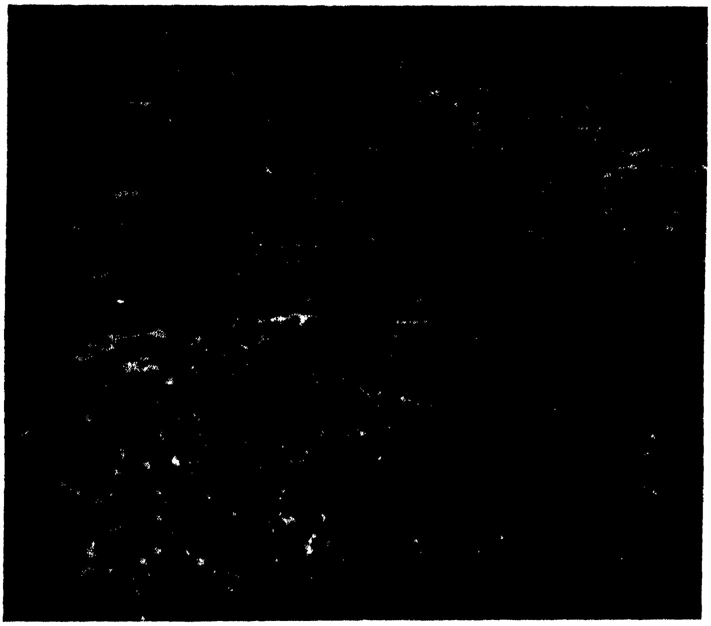

FIG. 491. *Addison's disease—atrophic suprarenal.* This is a portion of a much atrophied and fibrosed suprarenal. Only small islands of cortical cells remain ; many of these are undergoing atrophy with infiltration of lymphocytes around them. × 100.

TUMOURS OF THE SUPRARENALS :—

Metastases of carcinoma or sarcoma occur frequently from any of the common primary sources, and particularly from bronchial carcinomas (Fig. 352, p. 574). Of **primary tumours,** two groups can be identified, one originating from cells of the medulla and the other from those of the cortex.

Tumours of the Medulla. As the medulla is of neurogenic origin, the tumours which arise from it may take the form of primitive neuroblasts—**neuroblastomas :** or be differentiated so as to be recognisable as nerve-cells, *i.e.*, as **neurocytomas** (called by some writers " ganglioneuromas " [1] : or be still further differentiated so that they give the reaction with chrome salts and even form adrenaline—**phæochromocytoma** (or " chromaffinoma ").

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[1] With regard to the word " ganglioneuroma " as a general term for nerve-cell tumours, *see* pp. 315 and 1114 to 1118. It is an ambiguous word, and its use is best avoided. If special names are desired for tumours arising from nerve-ganglia, or from the chromaphil paraganglia associated with the ganglia of the sympathetic trunks or plexuses, these may respectively be termed **" gangliomas "** and **" paragangliomas."**

Of these, the **neuroblastoma,** being the most primitive histologically, is the most malignant (Fig. 492). It is composed of small cells resembling lymphocytes but often arranged in clusters or " rosettes " which, by special histological methods, may show fine fibrils, the appearances closely resembling those seen in developing nerve-tissue in the fœtus. It is essentially a tumour of childhood, being rare in adult life. It gives rise to widespread metastases, which, however, may have a peculiar distribution depending on the differing lymphatic drainage of the two glands. Those occurring in the **right** suprarenal spread especially into the liver, which may be extensively infiltrated, and into the mesenteric lymph-nodes ; death usually supervenes before further metastases develop, though involvement of right pleura and of right cervical lymph-nodes, orbit and skull may occur. This picture gives " Pepper's syndrome." When the **left** suprarenal is the primary site, the spread is by lymphatics, which, in this instance, run to the lumbar nodes and *viâ* the cervical chain to the skull. Early secondary deposits are found in the orbit and in the skull-bones ; to this picture the term " Hutchison's syndrome " is sometimes applied. It may happen that the orbital tumour, causing proptosis of the eyeball, is the first indication of the condition, and only histological examination of the growth gives the clue as to its real origin.

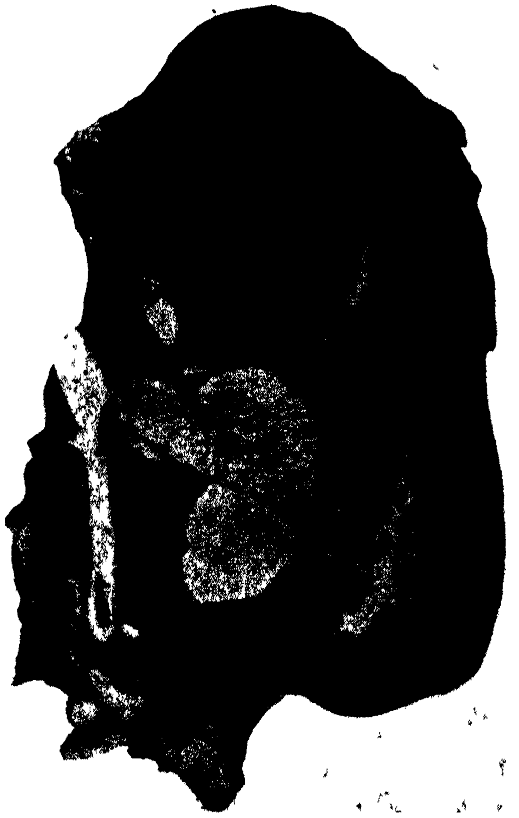

FIG. 492. *Neuroblastoma of Suprarenal.* The suprarenal is replaced by a large mass of tumour which is extensively hæmorrhagic. Secondary deposits occupy lymph-nodes at the hilum of the kidney.

The **neurocytoma,** when it arises either from nerve-ganglia or from the suprarenal medulla, is a more fully differentiated and less malignant tumour than the neuroblastoma ; though in some neurocytomas the cells may still retain a varying degree of malignancy. The cells composing these tumours are easily recognisable histologically as nerve-cells (*cf.* Figs. 700–704, pp. 1115–17), the more mature the type of nerve-cell, the more benign the resulting tumour.

The **chromaphil** (or so-called "chromaffine ") **tumour** or **phæochromocytoma** (*cf.* p. 222) is a growth affecting especially adults and is usually benign, although malignant varieties, giving rise to metastases, are recorded. Adrenaline (epinephrine), often in considerable amount, may be demonstrated in it and its cells give the specific chrome-reaction. Most of the recorded cases have shown a greatly increased blood-pressure, either as a constant feature or appearing paroxysmally. Death from cerebral hæmorrhage is not infrequent.

Tumours similar to those described may also arise from the various paraganglia which, as already noted (p. 842), are of similar embryonic origin.

Tumours of the Cortex may be benign—**adenoma**—or malignant—**carcinoma**—and may give rise to no special symptoms other than those of tumour as such; or they may be associated with effects which are the result of an excess of cortical hormone. The chief effects seen are those related to sexual characteristics.

If the tumour occurs before birth, pseudo-hermaphroditism may be found: a cortical hyperplasia alone may produce a similar result (Fig. 488 on p. 842A).

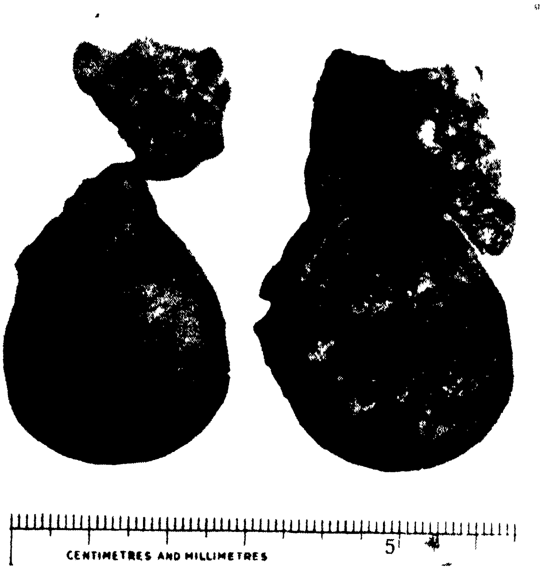

FIG. 493. *Simple cortical adenoma of right suprarenal* (almost natural size) from a woman of sixty-two years, who had become enormously stout. There was a similar tumour on the left side. The patient died after an operation for the removal of a meningioma of the right temporal lobe. (Dr. Colin Edwards' case, W.E.H.)

FIG. 494. A low-power of the tumour showing the microscopical characters of the groups of polyhedral cells, with small definite spherical nuclei in the faintly-stained reticulated cytoplasm. Mallory's connective-tissue stain. × 100

If in childhood, the result is precocious puberty with, in the male, pronounced development of the genitalia and secondary sex-characters. In the female, sexual development also is hastened but has the characteristics of "virilism," *i.e.*, "maleness"; the voice deepens, hair grows on the face and pubic regions, the clitoris enlarges, but the female genitalia fail to develop, and obesity is usually pronounced. After puberty, the occurrence of a cortical adenoma may be followed by no specific symptoms in the case of the male, but, in the female, "virilism" develops and menstruation ceases; hypertension is also a frequent accompaniment of these tumours. Thus at all ages the specific effect of cortical overgrowth is an imposition of male characters, even in the female.

It is of interest to note that many of the clinical features observed in patients with cortical suprarenal adenomas are seen also in cases of basiphil adenoma of the pituitary (Cushing's syndrome, pp. 815–17). Indeed, in the latter condition, hyperplasia or even adenoma of the suprarenals has been found in some cases. It is, therefore, necessary to exclude the possible presence of such a pituitary tumour before associating all the symptoms with the suprarenal. That an adrenal cortical adenoma by itself can be responsible for virilism would seem to be proved by the fact that its surgical excision has removed all the signs of virilism in the female.[1]

These cortical tumours vary from a few millimetres to many centimetres in diameter. They are of a light yellow colour and many contain lipoid in their cells which have a general arrangement in columns approximating to those of the normal cortex. More atypical forms occur, often with giant-cells varying in shape and size : these are a feature especially of the more malignant types of tumour. In the latter, metastases are common and may be widespread throughout the body in lymph-nodes and other organs.

The term " hypernephroma " has been previously applied to a tumour of the kidney, in the majority of instances, erroneously supposed to be of adrenal origin (p. 895).

Secondary changes, especially hæmorrhage, are common in all suprarenal tumours, both cortical and medullary.

PINEAL BODY (Epiphysis cerebri)

This is a small, reddish structure, about the size of a cherry-stone, situated in relation to the posterior part of the roof of the third ventricle, from which it projects downwards and backwards between the superior pair of corpora quadrigemina. It is developed from an evagination of the wall of the third ventricle, from which evagination in certain reptiles, a more or less rudimentary median or third eye originates. The pineal is relatively larger in the child than in the adult, and in the female than in the male. Its structure varies considerably in different cases, but it usually shows a number of saccular, or, in some cases, tubular spaces, containing epithelial cells, and with large capillary or sinus-like blood-channels between the spaces. Most of the cells show fine oxyphil granules, but some show basiphil granules. The stroma consists of neuroglia, and the whole is invested with a pial covering. The organ undergoes considerable retrogression after puberty. The follicles also very frequently contain aggregations of calcareous particles (the so-called " **brain-sand** " or " corpora arenacea "), which may sometimes be present in marked excess and provide a useful localising landmark in radiograms of the head. (*See also* pp. 238 and 1122–5.)

There is still uncertainty as to production of any specific hormone by the pineal. Sexual precocity (pubertas præcox or " macrogenitosomia præcox ") has been noted in a few children the subject of tumours of the pineal, but the same train of symptoms has also been recorded from lesions of the hypothalamus, involving particularly the corpora mamillaria, and any pineal tumour probably acts by affecting the nervous mechanism associated with the sexual functions.

The only pathological lesions of importance originating from this structure are certain **tumours.** These may be of the nature of simple enlargements, usually with excess of the gritty particles described above (corpora arenacea or so-called " psammomata "). The typical **pinealoma** has a fibrous reticulum in which are two types of cell, the larger parenchymatous cell of the pineal, and aggregations of smaller lymphoid cells (p. 1120 *et seq.*). **Cystic growths** also occasionally occur ; and **teratomatous** and **mixed tumours** containing cartilage and gland-like elements, sometimes combined with sarcomatous structure, have been described.

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[1] " A Case of Virilism associated with Suprarenal Tumour : Recovery after its Removal," by Gordon Holmes, *Quart. Jour. Med.*, 1924–5, **18,** 143. Consult also " The Adrenal Cortex and Intersexuality," 1938, by L. R. Broster *et al.*, and " Paranoid Psychosis with Adreno-genital Virilism successfully treated by Adrenalectomy," *Brit. Med. Jour.*, 1939, *ii*, 1220, by the same authors.

CAROTID BODY (Glomus Caroticum)

Knowledge of the function of the carotid bodies, as well as similar organs on the course of the aorta and in the nail-beds of the fingers and toes, is still imperfect, and some difference of opinion exists as to the interpretation to be placed on their histological appearances. They have a rich meshwork of blood-vessels, between which are groups or columns of large clear cells, while abundant nerve-fibrils (connected, in the carotid bodies, with the glosso-pharyngeal and vagus nerves as well as with the cervical sympathetic trunk) are demonstrable in the supporting fibrous stroma.

The only known pathological change of importance is tumour-formation. The **Carotid-Body Tumour**[1] has been called by many names, *e.g.*, "chromaffinoma," paraganglioma, neuroblastoma and perithelioma. While certain examples resemble the neuroblastoma of the retina, having cells arranged in "rosettes," the majority of these neoplasms show a structure similar to that of the normal carotid body, and the large clear cells may give the chrome-reaction, thus resembling the cells of the suprarenal medulla—hence the names "chromaffinoma" and "paraganglioma" (pp. 222 and 315). Adrenaline has, however, *not* been demonstrated in these cells. The arrangement of blood-vessels and cell-columns of both the normal carotid body and its characteristic tumour-formation suggests that the former represents a "glomus" and the latter a "glomangioma" (*see* next paragraph).

COCCYGEAL BODY (Glomus Coccygeum)

This is a "**glomus,**" *i.e.*, a specialised **arterio-venous anastomosis,** other examples of which are found in various subcutaneous situations, especially in the fingers and toes; and from them, in any of these situations, tumours may occasionally develop (p. 1134).[2] They are small, slow-growing and almost always benign, subepidermal tumours, now known as "**glomangiomas,**" first described in 1812 by Dr. William Wood, of Edinburgh, as "painful subcutaneous tubercles," and found especially on the extremities, *e.g.*, under the finger-nails, and characterised clinically by attacks of agonising pain and reflex sympathetic disturbance, relieved at once by surgical removal. They take the form of an angioma-like tangle of vascular channels or spaces, enclosed within a fibrous-tissue capsule, and each lined by a single layer of flattened endothelial cells which sometimes become swollen, surrounded and embedded in a stroma of fine collagenous fibres containing large clear "endothelioid" or "glomus-cells," together with smooth muscle-fibres and nerve-fibrils, both medullated and non-medullated.

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[1] Articles on these tumours, with references to the literature, will be found in *Surg. Gyn. and Obst.*, 1927, **45,** 209; *Jour. Path. and Bact.*, 1933, **36,** 13; *Amer. Jour. of Surg.*, 1938, **40,** 462.

[2] For details of glomus-tumours see "Tumors of the Neuromyo-arterial Glomus," by A. Purdy Stout, Columbia, *Amer. Jour. Canc.*, 1935, **24,** 255 (dealing with the painful little subungual tumours of these organs found especially in the nail-beds of the fingers). *See also Arch. of Path.*, 1937, **23,** 615: and Schmidt and Comroe, *Physiol. Rev.*, 1940, **20,** 115.

The word *glomus*, *glomeris*, neut., in Latin, signifies a wound-up ball of yarn or thread. The **glomus** is a sensory body containing chemo-receptors concerned with the regulation of temperature, respiration and blood-pressure, and highly sensitive to physiological variations and alterations in the CO_2 and O_2 tension or *p*H of the blood, especially anoxia, as well as to the presence of certain drugs and chemical substances such as acetylcholine (*see under* Myasthenia Gravis, p. 1245 *et seq.*), nicotine, or cyanide.

CHAPTER XXV

DISEASES OF THE URINARY SYSTEM

SECTION I

DISEASES OF THE KIDNEY

THE kidney is formed from two sources, the metanephric cell-mass and an outgrowth from the mesonephric (or Wolffian) duct. The mesonephros does not contribute to the adult kidney in man, although it exists as a primitive excretory organ in the fœtus. The mesonephric outgrowth becomes elongated in a cephalic direction to form the ureter, the pelvis and calices,[1] and, by a process of branching from the calices, the collecting tubules. The metanephric cell-mass differentiates to form the convoluted tubules which join up with the collecting-tubules. By a process of invagination of blood-vessels into the ends of the convoluted tubules, the glomeruli are formed.

CONGENITAL ABNORMALITIES OF THE KIDNEY :—

1. **Congenital Malformations.** The most important of these is a junction between the two kidneys. Each of the affected organs may be situated in its normal position, but, in the majority of cases, one or both may be displaced downwards. In the most usual form of this malformation—the **horseshoe-kidney**—the lower ends of the two organs are united across the vertebral column (Fig. 495). The uniting band is in some cases composed of true kidney-substance, often of considerable thickness ; whilst in other instances it consists of fibrous tissue in which there is no trace of glandular structure. *Each half of the fused mass is usually provided with a single ureter*, which passes down in front of the uniting bridge. Occasionally, however, one or both of the ureters may be double, either throughout the entire length, or more usually only towards the upper end. There are, as a rule, two distinct pelves, which are in almost all instances situated towards the anterior aspect of the combined organ (Fig. 495).

Less common forms of fusion are seen where the kidneys are joined at their middle, or the lower pole of one to the upper pole of the other (sigmoid kidney), or the two may be fused into a single irregular mass.

Sometimes the fused organs are considerably displaced, the mass lying, it may be, towards one side of the abdomen, or even at the brim or in the cavity of the pelvis.

2. **Abnormality in Number.** The presence of a third kidney is extremely rare. Occasionally, only one kidney is found—the so-called **Solitary Kidney.** When the other organ is *entirely* absent, the ureter and the renal vessels are also absent on the same side. In some instances, traces of the other kidney are present, and may be discovered by following the course of the vessels or ureter, which, in such cases, may be present though often atrophic.

The Solitary Kidney may be increased in size, but this is by no means essential. Its vascular supply is often abnormal, for example it may receive branches from the iliac or other arteries. In health, this single kidney may effectively carry on the work of renal excretion ; but, if from disease of any sort its function is interfered with, the results will naturally be more serious than if there were another kidney to aid in the process of excretion.

3. **Inequality in the Size of the Two Kidneys** may be a congenital condition arising from arrested development or from disease during intra-uterine life ; or it may occur later in life from disease, for example from the impaction of a calculus producing loss of function and atrophy on one side. Similarly, localised vascular lesions may interfere with the normal growth of the kidney in young subjects, or with the maintenance of its nutrition

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[1] "Calices" : as this word is derived from the Latin, *calix*, a cup (*cf.* its derivative "chalice"), and *not* from the Græco-Latin, *calyx*, a whorl of leaves, it should be spelt with an "i"—"calix," plural "calices."

in the adult. Other causes of inequality in the size of the two organs resulting from Tumours, Cysts, Inflammation, etc., are described under these headings.

4. **Abnormalities in the Shape of the Kidneys, and in the Origin or Distribution of their Blood-Vessels** are frequently found in conjunction with the foregoing conditions. Accessory renal arteries may be present in addition to the usual vessels. In some cases such an artery enters the lower pole and, crossing the ureter, causes kinking and obstruction of it, with consequent production of hydronephrosis. Accessory arteries can arise from the main renal artery, the aorta, or the iliac vessels and it is believed that their presence can contribute to the production of raised blood-pressure (p. 869). The genital organs, may or may not show associated abnormalities, for example, they may be rudimentary or even absent, on the same side as the affected kidney.

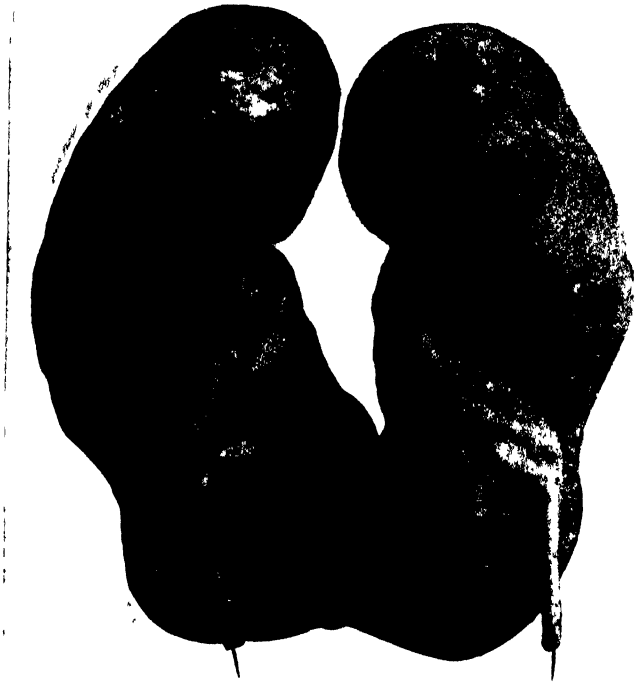

FIG. 495. *Horseshoe-Kidney.* The lower ends of the organs are united by a thick bridge of glandular tissue passing across the middle line of the body. The ureters (into which bristles have been inserted) pass down anteriorly.

5. **Abnormality in Position.** This is congenital or acquired. In **Congenital Malposition**—**ectopic** or **dystopic kidney**—all degrees of displacement are found, from cases in which it is comparatively slight to those in which the organ is situated just above, at, or even below, the brim of the pelvis. It may lie over the sacro-iliac joint, or in the hollow of the sacrum -**Sacral Kidney**. In the female, such abnormalities in position can lead to interference with parturition, and render the displaced organ liable to injury during the process. The corresponding suprarenal body usually is not associated with the kidney in such displacements, but is found in its normal position, and possesses its normal vascular supply ; whereas the origin of the vessels supplying the ectopic kidney is displaced downwards, *e.g.*, they may arise from the lower part of the aorta, the common or internal iliac, the middle sacral, or the inferior mesenteric artery. The kidney-tissue may be normal or diseased, and there may be associated defects in the bladder, rectum and genital organs, which, if unilateral, occur on the same side as the affected kidney.

Movable or Floating Kidney—Nephroptosis. All degrees of this condition are found, from a slight increase in the normal mobility up to cases in which the organ—most commonly the right—can be moved to almost any part of the abdominal cavity. This mobility is due usually to an abnormal laxity of the peritoneal and fascial investments covering the anterior surface, and of the fat and cellular tissue around the organ. The kidney may have an incomplete peritoneal covering, or may, in rare cases, even possess a complete investment and mesentery containing the renal vessels and ureter. In some cases, the condition appears to be congenital; but, in others, it is an acquired abnormality, the most frequent cause being repeated pregnancy, especially when combined with relaxation of the abdominal parietes, or where there has been absorption of the perinephric fat which helps to support the kidney in position. The condition is, therefore, found most commonly in women. The right kidney, as already stated, is more frequently affected than the left ; and it is very rarely that both organs are freely movable. Occasionally, the displaced kidney becomes adherent in some abnormal position ; or again, torsion of the vessels and of the ureter may occur.

6. **Persistence of Fœtal Lobulation** is common but is of little pathological importance. It is due to incomplete fusion of the lobular divisions in the fœtal kidney, which divisions should normally disappear. All degrees of this condition may be found, and, when slight, should not be mistaken for the depressions caused by the absorption of old infarcts, retention-cysts, etc. The capsule is adherent to the septa between the persisting lobes ; and such organs frequently show one or more medium-sized arteries penetrating the kidney-substance between these lobes.

7. **Abnormalities of the Ureters** occasionally occur, for example, doubling. This may be present on both sides, but more commonly it is on one side only (Fig. 41, p. 73). The ureters of that side may be separate throughout their course, with separate pelves and openings into the bladder, or they may fuse into one tube before reaching the bladder. The ureters may open into the rectum, or elsewhere, *e.g.*, into the seminal vesicles. The opening of the ureter may be congenitally absent, the accumulation of urine then leading to the production of hydronephrosis. The latter may also follow upon any congenital narrowing of the ureter where it originates from the renal pelvis : or upon atresia of its lower end—residual cyst-formation occasionally taking place from the remains of its lumen within the thickness of the bladder-wall. As noted previously, an accessory renal artery may cause kinking of the ureter (p. 851).

Congenital dilatation of one or, more usually, both, ureters, sometimes extreme in degree, is occasionally found, without any obvious cause and where no obstruction to the outflow of urine from the ureter itself, or from the bladder, can be demonstrated *post mortem*. Such cases are due probably to disturbance of nervous mechanism, either centrally or peripherally, causing spasm of the bladder-sphincter.

8. **" Inclusion " of Suprarenals.** This may vary from partial adhesion or fusion of the suprarenal body up to its total inclusion within the glandular substance of the kidney. Abnormal portions or supernumerary suprarenals may occur as inclusions within the kidney, the main suprarenal body being found in its usual position. Many small yellow portions of tissue which to the naked eye resemble suprarenal rests prove, on microscopical examination, to be small adenomas of renal, *not* suprarenal, origin. These may, later, become the site of more active carcinomatous proliferation (p. 895).

9. **Cystic Disease of the Kidney.** (Synonyms : **Cystic** or **Polycystic Kidney, Cystic Degeneration of the Kidney.**) Two varieties of cysts in the kidney are found, viz., (1) those which are primary, and apparently congenital ; and (2) cysts which are secondary to other diseased conditions. It is to the former of these that the term " cystic kidney " is specially applied. This condition may be found well advanced in the fœtus *in utero,* and may, owing to the large size of the affected organs, sometimes cause obstruction to parturition, and necessitate the evisceration of the fœtus. The disease is not confined to any special age, but may be found even in old persons, *i.e.*, such patients may

survive to old age. If uncomplicated by other renal disease, it may give rise to no definite symptoms during life, and kidneys showing advanced cystic disease may be found on post-mortem examination where its presence had been unsuspected during life. It is difficult, however, to affirm positively that, in every instance, the condition has been a congenital one, and has not developed during extra-uterine life. The disease is slowly progressive, and always affects **both** organs, though sometimes not to a similar degree. The kidneys

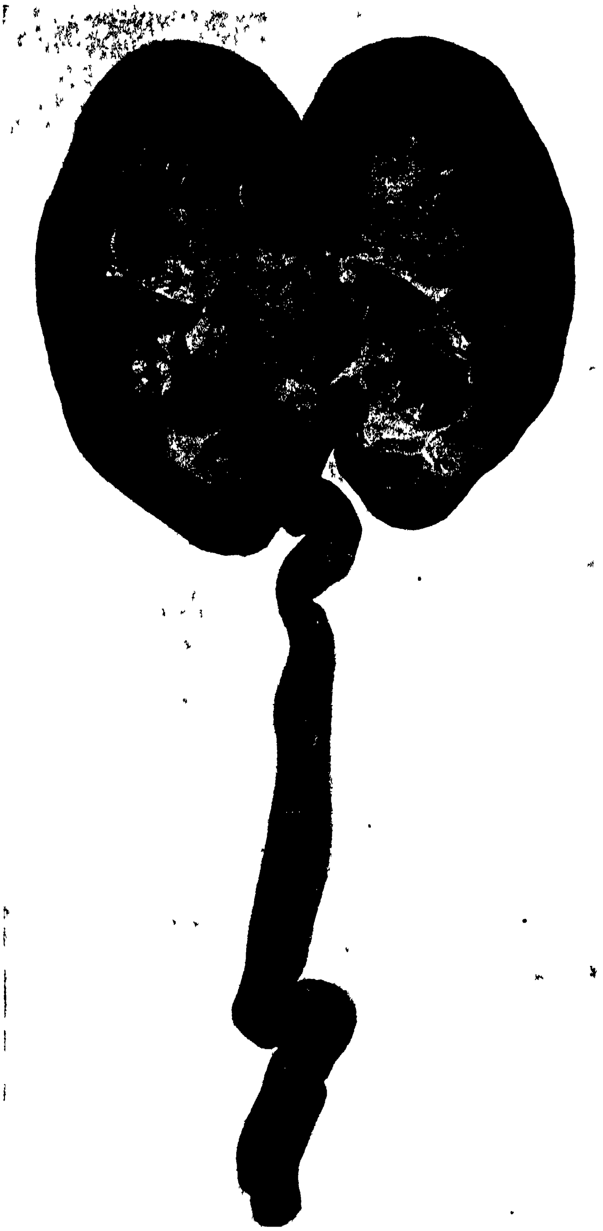

FIG. 496. Hydronephrosis arising from twisting and abnormal kinking of the ureter (*see* p. 892).

may be greatly enlarged, *e.g.*, they may measure some 6 to 8 or 9 inches in length, the general shape of the organ being usually preserved. Projecting from the surface, and studded throughout the substance of the kidney, are innumerable cystic spaces, varying in size from some which are just visible to the naked eye, up to those of several centimetres in diameter (Fig. 497). They are lined by a layer of simple, flattened epithelium, and their contents—which may be fluid, mucoid, or colloid in consistence—vary in colour, and may be clear and colourless, yellowish, or brown or reddish-brown from the presence of altered blood-pigment. Most of the cysts do not contain any of the special urinary constituents, though traces of urea may be found in some of them. Although, on naked-eye examination, there may appear to be almost no normal secreting glandular tissue left between the cysts, yet **microscopically** a considerable amount may be found stretched and distended around them. In most instances, there is sufficient kidney-substance present to enable the organs to carry on their functions more or less efficiently. In other instances, uræmia may supervene, either from the progress of the disease itself, or from some intercurrent affection of the organs themselves. Not infrequently the progressive increase in size of the cysts and consequent atrophy and fibrosis of the intervening renal parenchyma result in death from renal insufficiency in the fifth or sixth decade of life.

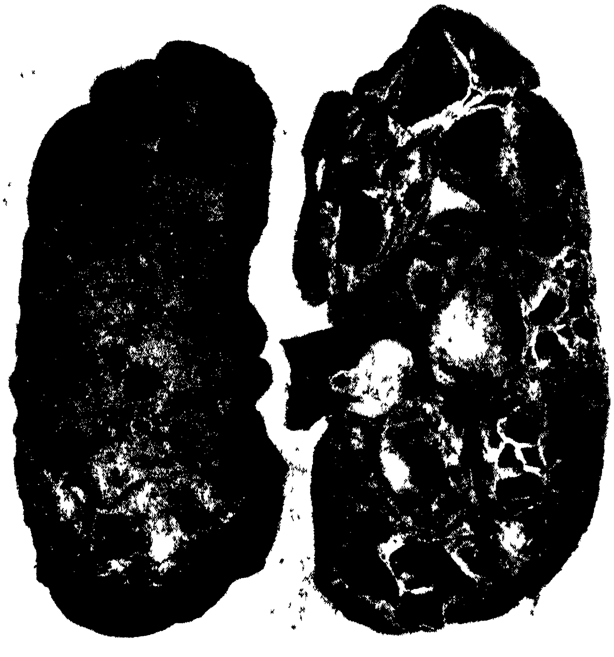
A. B.

FIG. 497. *Cystic Kidney.* A. Outer surface. B. Section.

Ætiology. Several hypotheses have been suggested with regard to the causation of the condition. Virchow was of opinion that it was caused by inflammatory changes and interstitial overgrowth of fibrous tissue, leading to compression of the tubules and to their subsequent distension above the sites of constriction, *i.e.*, a form of chronic interstitial nephritis. This explanation appears unlikely, both from the clinical, and from the histological, study of such cases. Other pathologists consider that it is produced by "embryonic intermingling" of the meso- and meta-nephros –the primitive and the permanent excretory organs respectively—which are developed in close proximity to one another. A third suggested explanation is that, early in development, some of the branching collecting-tubules arising from the outgrowth of the mesonephric duct fail to make connection with the secretory tubules growing from the metanephric cell-mass (pp. 353–4 and 850). The latter tubules thus end blindly, and, having no outlet for their products, dilate to form cysts.

It is not uncommon in cases of cystic kidney to find an associated cystic condition of the liver, or, more rarely, of the pancreas, and it may also occasionally occur as part of the syndrome of Lindau's disease (p. 1131).

INJURIES OF THE KIDNEY

Contusion and rupture of the kidney may result, **without external wound,** from a direct blow on the loin or over the lower ribs, or from indirect violence such as a fall upon the buttocks or forcible flexion of the body, or from the blast of explosions. The capsule may or may not be involved in the tear, and the effusion of blood and urine will be subcapsular or extracapsular accordingly. Lacerations may be of all degrees, from a slight crack to an extensive tear, and are usually transverse or slightly oblique, and most frequently on the anterior surface. The pelvis and renal vessels may be involved, and the ureter may be ruptured, with varying results. The commonest symptoms are **shock,** usually severe, but sometimes in slighter cases delayed, **pain, swelling, and hæmaturia.** Healing of lesser degrees of rupture usually occurs rapidly by vascularisation and organisation of the extravasated blood, with formation of fibrous tissue, the contraction of the latter resulting in a scar resembling that of an old infarct. In some cases, blood-clot may block the ureter, leading to traumatic hydronephrosis, which may also result from cicatrisation of fibrous tissue. Bacterial infection sometimes supervenes in such cases, either from below or *viâ* the blood-stream. Injury to the kidney in association **with an external wound,** *e.g.*, due to stabs or bullet-wounds, is almost always accompanied by infection, and, in addition to hæmorrhage and escape of urine, prolonged suppuration may follow.

STRUCTURAL CHANGES IN THE KIDNEY IN DISEASE

In the various **vascular, inflammatory,** and **degenerative diseases** to which the kidneys are specially liable, **both** organs are almost invariably affected—though not necessarily to the same extent or degree—as, from their anatomical relations and physiological functions, they are subject to practically identical conditions, for example, the necessity of excreting from the blood certain substances, normal or abnormal, which may have an irritating and deleterious effect upon their complex and delicate structure. All the component tissue-elements of the kidney may be, and most commonly are, affected simultaneously throughout the organ, though usually in varying degree. Thus, in some cases,

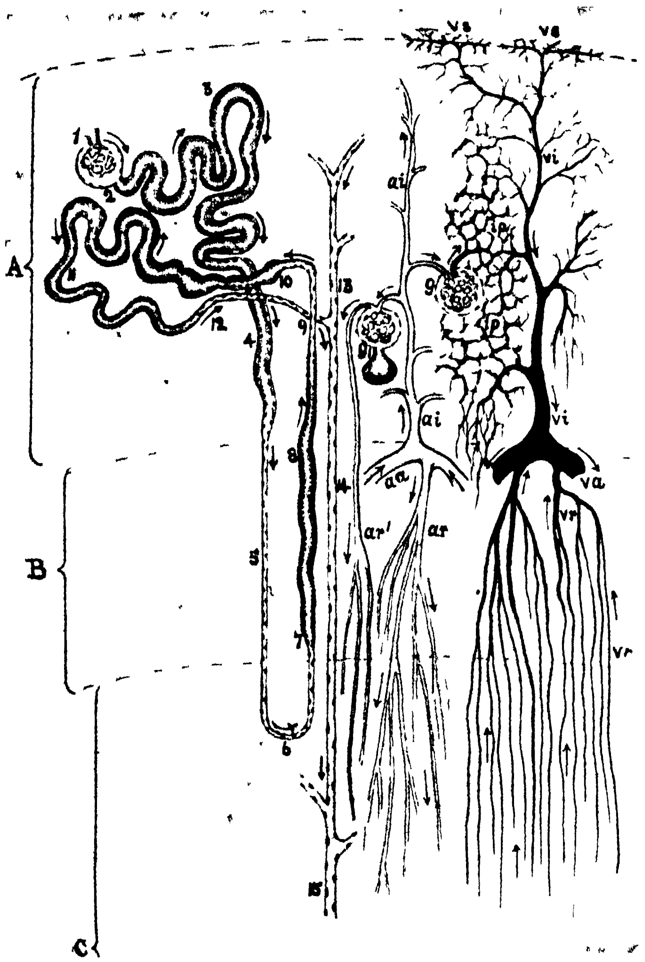

FIG. 498. *Diagrammatic representation of the Structure and Blood-Supply of the Kidney.* A, cortex : B, boundary zone : C, medulla.

TUBULAR ARRANGEMENT :—

(1) Bowman's capsule enclosing glomerulus. (2) Commencement of (3) first convoluted tubule. (4) Spiral tubule continuing into (5), descending limb of loop of Henle, (6), (7), (8) ascending limb of Henle's loop, becoming narrower at (9) to continue as second convoluted tubule (10), (11), which, by the junctional tubule (12), enters the collecting tubule (13), (14), (15).

VASCULAR DISTRIBUTION :—

(*aa*) Arterial renal arches giving off interlobular arteries (*ai*), which by afferent arterioles enter glomeruli (*g*) and by straight arterioles (*ar*) reach the medulla. The efferent vessels emerging from the glomeruli break up into the intertubular plexus of capillaries (*ip*) and send an occasional twig (*ar'*) to the medulla. The intertubular plexus unites to form the interlobular veins (*vi*), which also collect blood from the stellate vein (*vs*) on the surface, and finally end as the venous renal arches (*va*). From the medulla, blood is returned to the renal arches by the straight venules (*vr*).

In some cases there is a small vessel (Ludwig's) coming from the afferent arteriole and going directly to the intertubular plexus, thus short-circuiting the glomerulus.

the glomeruli show relatively greater changes than the other structural elements, whilst, in other instances, either the tubules, the vessels, or, it may be, the interstitial tissue, exhibit pathological changes which are relatively more pronounced in any one of them than in the others. In order properly to understand these pathological variations, it is of importance to have a clear conception of the normal structural arrangement of the kidney. (Fig. 498.)

The kidney is built up of an enormous number of what may be regarded as elongated glands or gland-units—each of which may be termed a "nephron"—closely packed side by side, each with its base at the surface of the organ, and its apex at the summit of one of the Malpighian pyramids, the whole organ being invested by a strong but thin and transparent, comparatively non-adherent, fibrous membrane or capsule. All these kidney-elements, primitive cones, or nephrons have a similar structure, each being grouped around its corresponding collecting tubule.

Summary of Functional Activities of the Kidney. Without entering into the controversies of the subject, the following is a brief account of what may be regarded as reasonably established.

The functions of the kidney are : (*a*) to excrete waste-products or foreign substances from the blood, (*b*) to regulate the water-content of the body, (*c*) to regulate the acid-base equilibrium of the blood and tissues, (*d*) to conserve substances of use to the body.

These functions are carried out by several mechanisms usually operating together. Blood is carried to the glomeruli and circulates through the capillary loops under a blood-pressure sufficient to cause a simple physical filtration of water with dissolved substances through the walls of these vessels and the covering epithelium of the glomerulus. Only substances of sufficiently small molecular size are carried through with the water, thus protein molecules do not pass, whilst those of such substances as urea, uric acid, creatinin, salts of sodium, potassium and magnesium, and glucose pass freely. As this filtrate passes down the tubular system, two things commonly happen : (1) Water is reabsorbed owing to the higher osmotic pressure in the intertubular capillaries, and with the water a certain amount of the dissolved substances. In addition to the absorption of water, there may be active reabsorption of some of the solutes, *e.g.*, glucose, so that none of these appears in the bladder-urine. (2) The tubules, in addition to reabsorbing, may actually excrete substances, so that the concentration of these is raised in the final urine. This last mechanism is the chief excretory function in the non-glomerular kidney of certain fishes. In the higher mammals and man, the filtration-reabsorption activities rather overshadow those of tubular excretion, though it can be demonstrated with regard to some foreign substances such as phenol-red. Smith (*loc. cit.*) has shown that inulin is filtered by the glomeruli and neither actively reabsorbed nor excreted by the tubules, and he has, therefore, used it as a standard for glomerular filtration. Glucose, which is filtered in solution with the water, is, normally, totally reabsorbed ; under the action of phloridzin, glucose appears in the urine owing to phloridzin inhibiting tubular reabsorption.

The term "Clearance" is commonly employed to express the excretory activity of the kidney ; it indicates the amount of a substance removed by the kidney from the blood in unit time. Thus "urea-clearance" is obtained by dividing the product of the concentration of urea in the urine (U) and the volume of urine formed per minute (V) by the concentration of urea in the blood, or plasma (B or P), and may be expressed :— $\frac{UV}{B \text{ (or P)}}$. Conversely, "the clearance is also the minimum volume of blood required to furnish the quantity of substance excreted in the urine in one minute's time" (H. W. Smith, *loc. cit.*).

Water-regulation is carried out mainly by variation in amount of tubular reabsorption ; and the same applies to acid-base regulation, though in the latter case the concentration of acid or basic substances in the blood determines their corresponding excretion in the urine. The pituitary furnishes a hormone—the "anti-diuretic" factor or hormone—which by its action on the kidney facilitates the reabsorption of water by the tubules. This hormone is controlled by a rather complicated mechanism in the hypothalamic region of the brain (*see also* under Pituitary, p. 807, *et passim*). Diabetes insipidus is due to lack of this hormone, and is caused by interference with the secretion of the pituitary itself or with its hypothalamic nervous-control mechanism.

Under normal conditions, there is an intermittency of action of glomeruli. Under pathological conditions, filtration may be impeded in the glomeruli, as in acute and some forms of subacute nephritis, or the filters may be reduced in number, as in chronic nephritis and severe arteriolosclerosis. Absorption may be increased, as in some forms of subacute nephritis ("nephrosis") in which, with the same blood-flow as normal, most of the glomeruli are in action simultaneously, but are passing less fluid which is exposed to a relatively larger area of tubule. Abnormal absorption may occur, as in "nephrosis," in which lipoid may be passed by glomeruli and reabsorbed into the cells of the tubules. Absorption may be reduced where the tubule-area is damaged, *e.g.*, in poisoning with a substance such as corrosive sublimate, which attacks the tubules especially ; or where the tubule-area is reduced, as in chronic nephritis.

The naked-eye appearance of the kidney may sometimes give an idea of the nature of its pathological changes, but often comparatively little gross change is visible with even serious lesions. Microscopical examination is, therefore, essential for the adequate investigation of all specimens.

The structural changes—more particularly those in nephritis—in the various elements of the nephron or kidney-unit are described under the individual diseases of the organs.

DEGENERATIVE AND PIGMENTARY CHANGES

1. **Cloudy Swelling and Fatty Degeneration.** These have been dealt with in detail elsewhere (pp. 190 and 194). The structural elements specially affected in the kidney are the convoluted tubules ; fatty degeneration may also be seen in the glomerular tufts, in the cells of Bowman's capsule and in the walls of afferent arterioles.

2. **Glycogenous Infiltration** (p. 207). In diabetes mellitus and in the rare condition of von Gierke's disease, there may be accumulation of glycogen in the convoluted tubules, especially in the ascending loops of Henle. In von Gierke's disease (p. 207), there are abnormally large accumulations of glycogen in liver-cells, heart-muscle and voluntary muscle ; the ætiology of the condition is obscure.

3. **Amyloid Degeneration** (pp. 210–11 and 886). This may occur in a previously healthy kidney or may be superimposed on an already damaged organ, *e.g.*, a chronic nephritic kidney. The appearances will differ in such cases, in the former the kidney will be large, pale and "waxy," in the latter the characters of the chronic nephritis—granularity, atrophy, etc.—may obscure the amyloid change, unless specially stained.

4. **Hyaline Degeneration (or Infiltration)** (pp. 214 and 868). It occurs especially in the afferent arteriole and in and around the walls of the glomerular capillaries.

5. **Pigmentary Deposits** (p. 218). **Bile** produces staining of the kidney in cases of jaundice, and the bile-pigment may be found microscopically as granules or crystals in the tubules and also in the interstitial tissue. **Blood** (p. 223)—In cases of severe blood-destruction, *e.g.*, blackwater fever and paroxysmal hæmoglobinuria, blood-pigments may be found in the tubules, sometimes forming casts. Pigment may occur also in the convoluted tubules. This is well seen in Addisonian ("pernicious") anæmia (p. 652), in which the kidney, to the naked eye, may have a rusty-brown colour and gives the Prussian-blue reaction for iron.

6. **Calcium** (p. 237). In cases where the blood-calcium is high, *e.g.*, in excessive parathyroid activity, or when excessive doses of vitamin D are given, there may be deposits of calcium in the cells of the convoluted tubules and in their lumina. Calculi may be formed by accretion of such particles in the pelvis of the kidney. In corrosive-sublimate poisoning, necrosis of convoluted tubules is produced and calcium is deposited in the dead tissue (p. 868). Old infarcts may become calcified.

7. **Urates** may be deposited in the apices of the pyramids in the new-born, giving the so-called "uric-acid infarct." In gout and also in some cases of chronic nephritis, deposits of urates are found, mainly in interstitial tissue, and may show, to the naked eye, as yellow, chalky streaks or patches.

8. **The Occurrence of "Casts" in Renal Disease.** Collections of solid or semi-solid material, *e.g.*, cells, fibrin, etc., may fill the tubules, and form cylindrical casts in them. These casts may be seen, microscopically, ***in situ***, in sections of the kidney; or they may be found in the urine.

With regard to the latter, a study of Fig. 498, p. 856, will suggest to the reader that their usual origin must be the collecting-tubules and the uriniferous ducts of Bellini; whilst it is unlikely, if not a physical impossibility, for casts formed higher up in the nephron, *e.g.*, in the convoluted tubules, to be washed down entire and unbroken and found, as such, in the urine; though there is no reason why single or even small groups of epithelial cells, as well as red blood-corpuscles, cannot be carried down into and be found in the urine—or become embedded and incorporated in any casts in process of formation in the collecting tubules and ducts, and so be washed out in and along with these into the urine. Nevertheless, most of the cellular casts found clinically in the urine are almost certainly formed in, and derived from, the collecting tubules.

Varieties of Casts :—

1. **Those composed of altered tubular epithelium :—**
   - i. **Epithelial casts,** formed of desquamated epithelial cells, which are often mixed with leucocytes, fibrin, etc. These may undergo various degenerative changes, and be found as—
   - ii. **Colloid casts** (sometimes wrongly called "waxy"). When swollen, clear, and homogeneous, these form one variety of **hyaline casts.**
   - iii. **Granular casts,** where the cells are undergoing granular disintegration.
   - iv. **Fatty casts,** where they show fatty changes.
2. **Those composed of altered blood or inflammatory exudate :—**
   - i. **Blood-casts,** of altered or unaltered red blood-corpuscles.
   - ii. **Leucocyte-casts.**
   - iii. **Fibrinous and albuminous casts**—another variety of the so-called **hyaline casts** (*cf.* 1, ii).
   - iv. **Blood-pigment casts,** containing granules or crystals of altered hæmoglobin (hæmatoidin, etc.).
3. **Those composed of normal or abnormal urinary constituents, or other substances excreted by the kidney :—**
   - i. **Urates, uric acid,** etc.
   - ii. **Bile-pigment,** *e.g.*, bilirubin, in some long-standing cases of jaundice.
   - iii. **Calcareous casts,** due to calcification in necrotic epithelial or in other forms of casts.

CIRCULATORY DISORDERS OF THE KIDNEY

(*a*) **Active hyperæmia of the kidney** may be found in cases of convulsions, for example in epilepsy; and, in such patients, a transitory albuminuria and hæmaturia may occur. More commonly, however, this reaction occurs in the acute infective fevers, and with poisons such as cantharides, corrosive sublimate, arsenic or carbolic acid, and may then be regarded as either preliminary to, or as part of, an acute inflammatory attack.

(*b*) **Passive or venous congestion** may be **acute** or **chronic,** the latter especially being common.

Acute venous congestion can occur with great rapidity, for example in opium-poisoning, and in some cases of coma from other causes. In its most intense form, it is found as a sequel to obstruction of the renal vein from thrombosis, ligature, or torsion of the vessels of a floating kidney. The changes occurring in the organ are described on pp. 149 and 155. Thrombosis of the renal vein may be produced by direct extension into it of a thrombus in the inferior vena cava, or by the pressure of a tumour on the vein. If the renal artery remains patent, intense congestion occurs, usually accompanied by hæmorrhages into the glomeruli, the tubules, and perhaps also into the pelvis of the kidney.

Chronic venous congestion of the kidney is common and is due, in the majority of cases, to **old-standing heart disease,** especially to lesions of the mitral valve, the condition being sometimes termed "**cardiac kidney.**" Chronic venous congestion may also, but much more rarely. be produced by local interference with the venous return, as, for example, by the pressure of a tumour upon the renal vein or on the inferior vena cava, or from mechanical displacements of the organ, as in floating kidney.

The naked-eye appearances of the kidney vary considerably if other lesions are associated with the chronic venous congestion. In an uncomplicated case, the organ is usually moderately enlarged. Its capsule may be slightly thickened and somewhat adherent, and the cortex shows at first some increase in volume ; but at a later period a certain degree of atrophy, especially in its inter-pyramidal portions, takes place. This atrophy is due to interference with the nutrition and functions of the tubules, and leads to the production of a slightly granular or morocco-leather-like surface. **On section,** the larger veins are dilated, whilst the engorgement of both sets of tributaries of the venous renal arches maps out the minute naked-eye structure of the organ very distinctly. The venulæ rectæ stand out prominently as dark-red radiating lines, which are most marked towards the bases of the pyramids ; whilst, in the cortex, the alternation of the pale medullary rays with the engorged lines of the interlobular vessels can be seen. If the dark lines corresponding to the engorged interlobular veins be closely examined, the glomeruli can be seen as minute, dark-red dots, giving a finely-stippled appearance to the vascular markings. The stellate veins on the surface are congested, and the organ is distinctly firmer in consistence and darker in colour than normal.

On microscopical examination, the pathological appearances are best seen at the bases of the pyramids in the bundles of straight venules, the walls of these being thickened and their lumina distended with blood. The glomeruli are enlarged, the capillaries being dilated and their walls thickened. Similar dilatation and thickening are seen in the interlobular veins and intertubular capillary plexus. The increased firmness of the kidney is due to this engorgement of the veins and capillaries and to the thickening of their walls, and not to proliferation of the connective-tissue framework of the organ. Some degree of atrophy may supervene in the tubular epithelium, and catarrhal changes, especially in the collecting tubules, may be present. In uncomplicated cases, however, such structural changes are not specially pronounced. Minute hæmorrhages from the glomerular tufts sometimes occur, and the blood may, in severe and advanced cases, find its way into the tubules and be passed into the urine. As a rule, however, such hæmaturia indicates the presence of some complication, especially the occurrence of embolism and infarction, conditions not infrequently associated with chronic venous congestion arising from mitral disease.

(c) **Embolism and Infarction.** These conditions and the characteristic lesions produced by them are described on pp. 167 and 172–5. Infarcts of various sizes and at various stages—from those newly formed to those which have become completely absorbed and show merely as puckered and depressed fibrous-tissue scars—may occur in the kidney. The occurrence of **septic embolism** and **abscess-formation** in ulcerative endocarditis and in pyæmia from other causes is discussed under **Suppurative Nephritis** on p. 862.

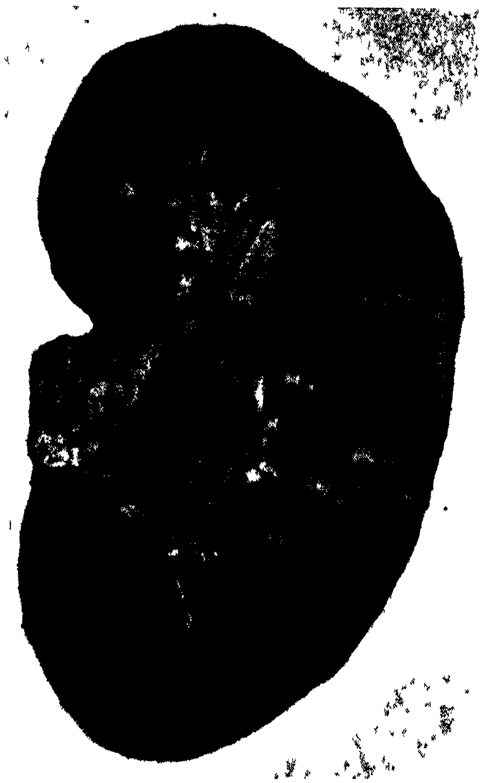

FIG. 499. *Bilateral Cortical Necrosis* The necrotic areas are pale and confined to the cortex, both superficial and interpyramidal , they are defined by a dark margin which represents intensely engorged capillaries.

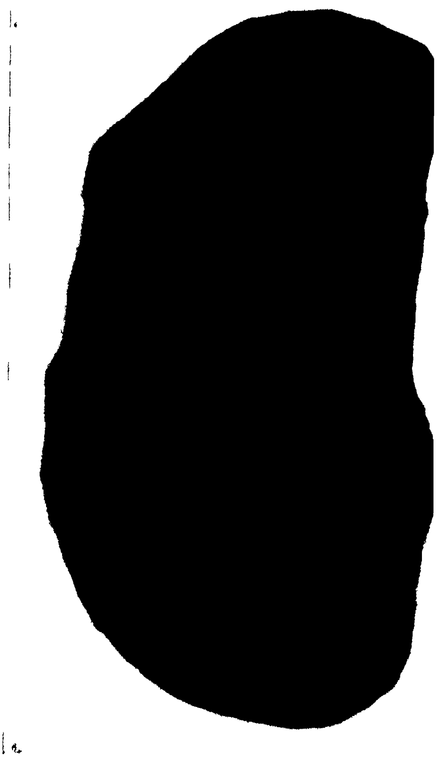

FIG. 500. Kidney from a case of myeloblastic leukæmia Numerous hæmorrhages, indicated by the dark spots, are seen on the outer surface of the kidney (p 631).

Bilateral Cortical Necrosis. This is a rare condition, which may occur in pregnancy, although it has been recorded in other conditions. It is sometimes associated with eclampsia or with uterine hæmorrhage. The onset is sudden and the prominent feature is anuria, or, perhaps, the passage of only a few cubic centimetres of urine containing albumin and often blood. Both kidneys show extensive necrosis of the cortex, the affected areas being surrounded by a congested zone (Fig. 499). Microscopically, the appearances are those of infarction ; and thrombosis has been found in the interlobular arteries and afferent arterioles. The cause of the condition is unknown ; the thrombosis found may be due to vascular spasm or to some undefined toxin associated with the pregnancy. Its occurrence has also, in certain rare instances, been reported in males.

(*d*) **Hæmorrhages** into and from the kidney—apart from traumatic causes such as rupture or penetrating wounds—frequently occur in intense toxic poisoning, especially when this is characterised by acute venous engorgement. Such extravasations of blood are usually comparatively slight. They are found especially in or around the glomeruli and in the tubules. Hæmorrhages into the interstitial tissue are comparatively rare. They may originate from the subcapsular vessels, and from the straight vessels in the boundary zone. More severe hæmorrhages, especially from the mucous membrane of the pelvis, tend to occur in **purpura, scurvy,** the **leukæmias,** and other "blood-diseases." Bleeding, often intermittent and varying greatly in amount, may also take place as a result of the presence of tumours and calculi. Faint traces of blood in the urine are a not uncommon accompaniment of the irritation of oxalate crystals. Minute submucous petechial hæmorrhages are of common occurrence in many acute toxic and septicæmic diseases; and an **intense hæmorrhagic nephritis** may in certain cases supervene in some of the acute infective fevers, *e.g.*, epidemic cerebrospinal meningitis. For the hæmaturia of "blackwater fever," *see* p. 659.

(*e*) **Myohæmoglobinuria** (p. 1242). After severe crushing and other lesions, involving extensive destruction of **muscle,** hæmoglobin, believed to be derived **from the muscle-substance,** may be found in the urine, accompanied by clinical symptoms suggestive of acute tubular nephritis.

INFLAMMATORY CONDITIONS OF THE KIDNEY

1. **SUPPURATIVE NEPHRITIS.** Pyogenic bacteria find their way to the kidneys by means of the blood-vessels, the lymphatics, the urinary passages, or, directly, by traumatic lesions. In ulcerative endocarditis or in pyæmia from other causes, minute abscesses form in the kidney-substance, owing to the impaction of small septic emboli, originating from a breaking-down septic thrombus in a vein, or from an infective vegetation on one of the heart-valves. These abscesses are found throughout the kidney-substance, but, owing to the fact that the emboli are generally small in size and therefore tend to be caught in the smaller branches of the arteries and in the glomerular and intertubular capillaries, they are seen especially along the lines of the vessels in the cortex, frequently exhibiting a radial appearance corresponding to the distribution of those vessels. They are found also along the arteriolæ rectæ in the medulla, and even around some of the larger branches of the renal artery. **On microscopical examination,** a minute thrombosed artery or capillary, containing a dark-staining plug of organisms, most commonly staphylococci or streptococci, can usually be found in the centre of such an embolic abscess (Fig. 502). Around this little vessel, if the embolism has occurred a sufficient length of time before death, intense necrotic changes are seen in the neighbouring kidney-tissue, the structural characters of which become lost. The necrotic area shows diffuse staining with the acid dye (*e.g.*, eosin), and an infiltration with leucocytes, chiefly of polymorphonuclear type. At a later period, softening supervenes and minute abscesses are formed, which tend to be elongated in the line of the vessel concerned. Neighbouring abscesses may coalesce,

giving rise to lines of more diffuse suppuration. When the septic emboli have become impacted only a short time before death, plugs of micrococci can be found in some of the vessels, with little or no inflammatory reaction around them.

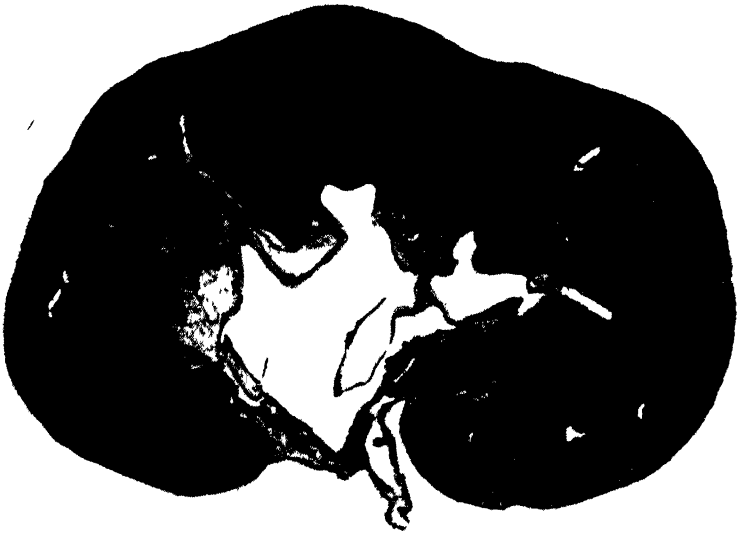

Fig. 501. *Pyelonephritis.* A large stained section of kidney to show lines of infection radiating out from the apex of a pyramid to the cortex.

Fig. 502. *Abscess in the kidney,* showing darkly-stained central embolic plug of bacteria in a small artery, with surrounding mass of leucocytes. Gram-Weigert method. × 50.

Another and common variety of suppurative nephritis is that due to the spread of infection from below, by way of the urinary passages or by their lymphatic channels—variously denominated "**consecutive nephritis,**" "**surgical kidney,**" or, from the fact that the pelvis is involved as well as the substance of the kidney, **suppurative pyelonephritis.** The second of these terms arose from the frequency with which the infection of the kidney supervened upon surgical interference with the urinary passages—especially the use of the catheter—in the days before asepsis was understood and practised. This form of suppurative nephritis is specially common in conditions which produce or lead to cystitis : for example, paralysis of the bladder in lesions of the spinal cord (p. 899), the irritation of calculi, gonorrhœal infection, the passage of a non-sterile catheter, or when the meatus and anterior part of the urethra have not been washed out with antiseptic before catheterisation. The kidney is generally infected by the spread of a catarrhal change up the ureter to the pelvis. In the renal pelvis, the earliest naked-eye manifestation of the inflammation is found usually in the little pouches where the calices surround the papillæ. A suppurative pyelitis may develop, and this may spread to the kidney-substance and become a pyelonephritis. In some cases, the condition starts in the pelvis of the kidney itself, *e.g.*, when it is the seat of calculus-formation. The exact route by which the infection reaches the kidney-tissue probably varies in different cases. There are three available channels of infection, viz., the blood-vessels, the lymphatics, and the uriniferous tubules, and all three may, in a given case, take part. The minute abscesses characteristic of the condition are distributed along the lines of the vessels, but there may also be plugs of pus distending the collecting tubules, and, once infection has begun, it spreads to involve vessels, their accompanying lymphatics and adjacent tubules.

The **naked-eye** appearances of the kidney are, as a general rule, characteristic. The organ is swollen, softer, and more vascular than normal. On the surface beneath the capsule and along the lines of the vessels in the substance of the organ are seen small, whitish or yellowish-white points, arranged singly or in clusters, each surrounded by a zone of intense hyperæmia. These are scattered irregularly along the vessels, both in medulla and cortex, forming dotted, radiating lines, which sometimes extend from the apex of a papilla to the outer surface of the kidney. Both organs are affected, but often in varying degree ; and, associated with the condition, there is always intense catarrh of the mucous membrane of the pelvis and of its calices—**pyelitis**—usually most marked immediately around the papillæ of the pyramids.

Suppuration of the kidney may result from **trauma,** especially where there has been rupture of the renal substance or of a cyst.

PYELITIS or INFLAMMATION of the PELVIS of the KIDNEY. This may be **suppurative** or **non-suppurative.** Milder degrees of pyelitis may be due to the excretion by the kidney of irritants such as cantharides, turpentine, sandalwood, copaiba : or to acute retention, or chronic urinary obstruction. Pyelitis arises most frequently by direct spread of infection from the kidney-tissue above, or from the bladder and ureter below, though occasionally it is due to direct hæmatogenous infection. Bacteria may pass into the blood-stream from a tonsillitis, boil, carbuncle, pyorrhœa, or some other local infective conditions : or through the intestinal mucous membrane in constipation, catarrh or ulceration. In typhoid, paratyphoid, Mediterranean, and other infective fevers, the causal organisms are practically always present in the blood at some stage of the disease. Such organisms are removed from the blood by the liver and kidneys. In the case of the kidney, little local damage may follow, but, on the other hand, a pyelitis or pyelonephritis may be produced. It may occur in either sex and from a large number of infective causes, but it is particularly common in the female immediately after marriage, during pregnancy, or after parturition, and is due usually to infection with *Bact. coli.* Acute pyelitis is not uncommon in infancy and early childhood, especially in girls, and is often associated with intestinal trouble, especially constipation, or constipation with occasional attacks of diarrhœa. The commonest organism found in these cases is *Bact. coli,* but a combined infection of *Bact. coli* and *Streptococcus fæcalis* is also of such frequent occurrence that a routine search should always be made for the latter organism in all cases in which *Bact. coli* has been found, as the streptococcus is often present in much smaller numbers and its presence is overlooked. Streptococci and staphylococci, separately or together, are also fairly common, often along with diphtheroid and other bacilli of only secondary importance and of slight pathogenicity, but which tend to be persistent in their presence. Other members of the colon group, for example, capsulated organisms of " Friedländer " type, *Bact. lactis aerogenes* and *Bact. acidi lactici*—are also frequently found, either alone or along with *Bact. coli* itself, and the authors have also occasionally found paratyphoid bacilli. In certain cases, however, pyelitis arises from some cause in the renal pelvis itself, most commonly from the irritation of a calculus or calculi, or of oxalate crystals, with secondary bacterial infection ; congenital abnormalities, such as an abnormal renal vessel or narrowing of the ureter at its commencement may also be predisposing causes.

If suppuration is produced and the pelvis of the kidney becomes distended with the pus so formed, the term **pyonephrosis** is applied to the condition. As a result of this pyonephrosis, which may also be caused by suppuration supervening in a case of hydronephrosis (p. 894), the kidney becomes progressively destroyed—owing partly to pressure, and partly to an extension of the suppurative process into it—and may ultimately be represented by a sacculated bag of pus, the walls of which are formed by the distended pelvis and the capsule of the organ. Sometimes, especially if both kidneys are involved, death of the patient results, but, where only one organ is affected, the pus may become inspissated by absorption of its fluid constituents, leaving as a residue a white, or yellowish-white, plaster-like mass, in which calcification is liable to occur. In such a case it is sometimes difficult to determine whether this has originally been due to suppurative organisms or to tuberculosis.

Perinephritis and Perinephric Abscess. Inflammation of the tissues immediately around the kidney may be **suppurative** or **non-suppurative.** In the latter case, the condition may become chronic and lead to **fibrosis** of the fatty tissue around the organ, with adhesions to the capsule. The kidney has usually itself been diseased, and any form of chronic inflammation such as pyelonephritis, pyonephrosis, calculus or tuberculosis may be found. Lesser degrees of fibrosis of the perinephric fat may be due to vascular changes secondary to those in the kidney, described on p. 869 *et seq.* On the other hand, suppuration may occur in the loose fatty-areolar tissue around the kidney, which thus becomes embedded in an abscess, the organ itself, unless previously diseased, remaining free from involvement. Perinephric abscess may be due to the rupture of a cyst on the surface of the organ, or to the extension of an infective process from the pelvis or some other part of the kidney ; but, in many instances, the cause lies altogether outside the kidney itself. Thus the suppuration around the kidney occasionally arises during the course of typhoid fever, scarlet fever, measles or pneumonia, or as a complication of tonsillitis, carbuncle ; or it may be due to the extension of infection from neighbouring parts, *e.g.*, from tuberculous or other disease of the vertebræ or lower ribs, from an empyema burrowing downwards, or from the extension of an abscess in connection with the intestines or other abdominal viscera. In many cases, however, the cause is obscure. The commonest organisms found are *Bact. coli* or other organisms of coliform type, streptococci and staphylococci.

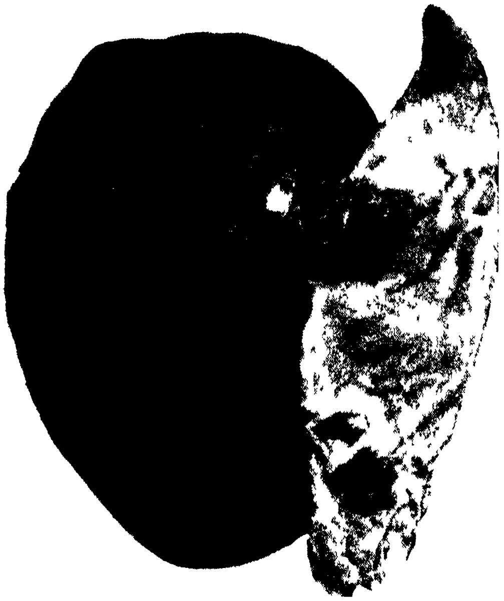

FIG. 503. *Perinephric Abscess.* Kidney from a case of pyæmia. Numerous small abscesses are seen on the surface of the kidney and several, notably a large one towards the upper pole, have ruptured through the surface and extended into and underneath the capsule which is shown reflected at the right.

II. NON-SUPPURATIVE NEPHRITIS :—

Under this heading will be considered those forms of renal diseases often included under the general term " Bright's disease," so named after Richard Bright of Guy's Hospital, London, who, in 1827, originally called attention to the association of diseased kidneys with œdema, hæmaturia, albuminuria and uræmia.

Unfortunately, the term " Bright's disease " is used to embrace a large group of renal conditions of differing ætiology and their effects, and is, therefore, apt to be vague in its pathological application. To those cases where the lesions fall primarily on the renal units as the result of exposure to infective or toxic agents, the term **nephritis** may be applied. In the cases where the damage is found primarily in the blood-vessels, from causes often unknown, the term **arteriosclerotic renal disease** may be used. While such a distinction is often possible, there are mixed cases where both changes are found and where it may be difficult to decide which has been primary. Indeed, in any given case it is not sufficient to observe the gross morbid anatomy and histology of the kidney, but, in addition, a knowledge of the clinical course and the chemical findings in blood and urine is necessary for a full comprehension of the morbid process or type of disease. In both the nephritic and arteriosclerotic groups, degenerative lesions occur and are sometimes the most obvious features ; the term **nephrosis** is often applied to certain examples of this (*see* later, p. 879).

Nephritis may be acute or chronic, with intermediate phases usually termed subacute, though the dividing line between these is often difficult to draw. Recovery from an acute attack may be complete, or the acute may merge into the subacute phase, and this in turn into the chronic ; or the onset may be insidious, and the disease not show itself clinically until already established in subacute or even in chronic form. Again, an acute attack may be superimposed on a chronic lesion, or a kidney may show different areas with different stages of damage. The damage may be **patchy** or **focal,** that is, confined to a limited number of nephrons : or **diffuse,** where the great majority of nephrons are affected. The effects of such differing distributions will be to give rise to cases of varying type from the clinical point of view. In all forms of nephritis, **both** kidneys are involved, though not necessarily always to an equal extent ; also **all** elements of the kidney are affected—glomeruli, tubules, interstitial tissue and blood-vessels—though the damage in any one of these may appear much more pronounced than in the others ; indeed, there may sometimes be no histological lesion demonstrable, although a functional, *i.e.*, clinical, defect must have been present, as shown by the chemical findings.

Ætiology of Nephritis. In many instances, the onset is insidious and no definite antecedent factor can be assigned as cause for it ; even in some of the acute cases, the exact causation may not be discovered. Many are associated with infection, especially streptococcal, *e.g.*, scarlet fever and tonsillitis. In these, it appears to be the toxin, rather than the organisms themselves, that is responsible for the lesions. In subacute bacterial endocarditis, due to *Streptococcus viridans*, focal lesions are found in the glomeruli (" focal embolic nephritis "), but it is often impossible to demonstrate cocci in these lesions. In acute ulcerative endocarditis due to hæmolytic streptococci, it is commoner to find infected infarcts containing organisms. Diphtheria may act, in virtue of its toxin, as a cause of nephritis. Pneumococcal infection has been described by Blackman (1934) as the cause of nephritis of the " nephrotic " type. Exposure to cold and " chills " are often given as causes of nephritis, but these probably act merely as accessory causes owing to the vasomotor changes they produce. Direct chilling of the kidney itself in the experimental animal may produce vaso-constriction with transient albuminuria and even hæmaturia.

Many chemical substances will produce renal lesions, mostly in the convoluted tubules. Bichloride of mercury causes tubular degeneration ranging from cloudy swelling to actual necrosis, the latter followed by calcification of the dead tissue (p. 858). Uranium nitrate, oxalic acid, potassium bichromate, cantharides and many other chemical substances act in much the same way by damaging the cells of the convoluted tubules, and occasionally causing glomerular changes such as congestion of the capillaries in the tuft and some swelling of the cells covering it and lining the capsule. These lesions resemble to some extent certain of the lesions occurring in the course of disease in man, where the tubules show the chief changes histologically, often termed " nephrosis " (*see* later p. 879). They do not correspond to those seen in the typical examples of nephritis occurring in man, where the glomeruli show definite lesions. A great number of experiments have been performed on animals in the attempt to reproduce nephritis. In addition to the chemical poisons mentioned, various bacteria and bacterial toxins have been used. Generally speaking, the bacteria produce infective lesions, sometimes gross infarcts or abscesses, or more diffuse inflammatory infiltrations. Toxins, especially diphtheria-toxin, produce tubular degeneration, and sometimes hyaline swelling of the glomerular capillaries with occasional capillary thrombosis.

From the fact that nephritis is commonly a late manifestation of bacterial infection (*e.g.*, scarlet fever), and that bacteria are not demonstrable in the renal lesions, it has been surmised that the lesion must therefore be of the nature of an **allergic response** in a tissue (the kidney) sensitised by previous exposure to the organism or its toxins. There is considerable clinical and experimental evidence in favour of this view. In animals sensitised by previous injections of streptococci, or of streptococcal toxin, subsequent injection of cocci, or toxin, directly into the renal artery caused more severe focal inflammatory reactions in the kidney than were obtained in non-sensitised control-animals.

Glomerular and tubular lesions closely resembling those found in human acute and subacute nephritis have been produced in the rabbit by means of injections into it of a " nephrotoxic " serum. This is obtained by emulsifying rabbit-kidney (previously perfused with saline to remove the blood) and making several injections of it into an animal of another species, *e.g.*, a guineapig. The serum of this animal contains a " nephrotoxin " for the rabbit.

The progressive nature of the renal damage in nephritis may be explained either by assuming that the kidney has been exposed through its vessels to repeated doses of a bacterial or other poison, or by assuming that previous exposure to bacterial or other protein products has sensitised the organ so that it reacts to subsequent doses of the same substances.

With regard to the ætiology of the primarily vascular form of nephritis—the arterio- or arteriolo-sclerotic kidney—it may be said at once that we do not know the cause. Whatever is responsible for the vascular damage is primarily the cause of the renal lesion. This form of renal lesion is associated with raised blood-pressure (" hypertension " or " hyperpiesis ") and the relation of this to the renal lesion has been the subject of much controversy and research.

Raised Blood-pressure in Renal Disease :—

In a primary renal lesion, a glomerulo-nephritis, there is, in many cases, moderate increase of blood-pressure in the acute stage. This may be brought about by the impeded glomerular circulation (*see* later, pp. 872 and 874) and by the hydræmia that is present in this stage. In many cases of subacute nephritis, there is no such rise of blood-pressure. In the chronic phase of glomerulo-nephritis (p. 877), raised blood-pressure is the rule. In this condition, the vascular area of the kidney is much reduced and the raised pressure may be regarded as compensatory, to keep up an efficient circulation through the organ.

Goldblatt and others (1934 and 1937), by graduated clamping of the renal arteries in dogs, produced hypertension (pp. 491–2). There are two possible explanations of this; either it may be a reflex hypertension induced by afferent impulses from the damaged kidney ; or the hypertension may be due to some pressor substance produced by the damaged kidney—but, so far, the nature of such a substance is still under investigation. Abnormally-situated renal vessels (p. 851) sometimes take part in the production of raised blood-pressure. It appears that the suprarenal cortex is necessary for the production of the experimental hypertension brought about by clamping the renal arteries.

In the hypertension of primary vascular disease—" essential hypertension " —various factors such as lesions of the pituitary or adrenal (*see* Chapter XXIV, pp. 806 and 840, *passim*) may be at work, these probably acting through the vasomotor mechanism. That the liability to this form may be familial is suggested by the occurrence of hypertension, with or without renal symptoms, in several members of the same family, and it has been demonstrated that some individuals react more vigorously than others to vasomotor stimulation.

Morbid Changes in Nephritis

The type or stage of nephritis is determined largely by the **focal** or **diffuse** character of the renal lesion and by its severity. Obviously, a focal lesion involving only some nephrons implies that other areas have escaped, or have been but slightly damaged, and are still able to function so that survival of the individual is possible ; such a case may thus become subacute, or chronic, even although the focal damage is severe.

The kidney has great reserve power and, normally, is probably never working to full capacity. If one kidney is removed, the remaining organ can do quite efficiently the work of both. In time it may even hypertrophy, especially in the young subject. Experimentally, it is possible to remove about three-quarters of the total renal tissue and still have efficient elimination on a normal diet. The **rate** of renal damage is important. A sudden widespread injury to many nephrons may produce rapid and serious functional disturbance, whereas the same, or even greater, damage if slowly produced may cause but little disturbance. This is due to the surviving units having time to adjust themselves to the altered conditions and, in some cases, to undergo hypertrophy and even hyperplasia.

Repeated focal lesions lead to progressive reduction of renal tissue and function, and, if not arrested, will lead inevitably to a fatal issue. Such focal lesions are apt to occur insidiously and, only when nephrons have been eliminated in numbers sufficient to interfere with function, will clinical evidence of renal disease appear. The "latent" forms of nephritis are, therefore, often focal in character.

On the other hand, a **diffuse** lesion, involving the great majority of the nephrons, will be rapidly fatal unless it is sufficiently mild to allow of the continuation of some function. Recovery may take place, or the disease may drift into a subacute or chronic phase, but the morbid changes in the kidney will differ considerably from those of the focal form.

Not infrequently, the renal lesion is overshadowed by major lesions elsewhere. For example, in bacterial endocarditis, there may be focal nephritis with clinical evidence of renal damage (albuminuria, hæmaturia, casts), but the patient succumbs to the cardiac disease or to embolism, before the renal lesion has time to become a sufficiently serious factor. Again, in some pneumococcal infections, particularly pneumococcal peritonitis, there may be renal involvement, but the peritoneal infection is the major factor.

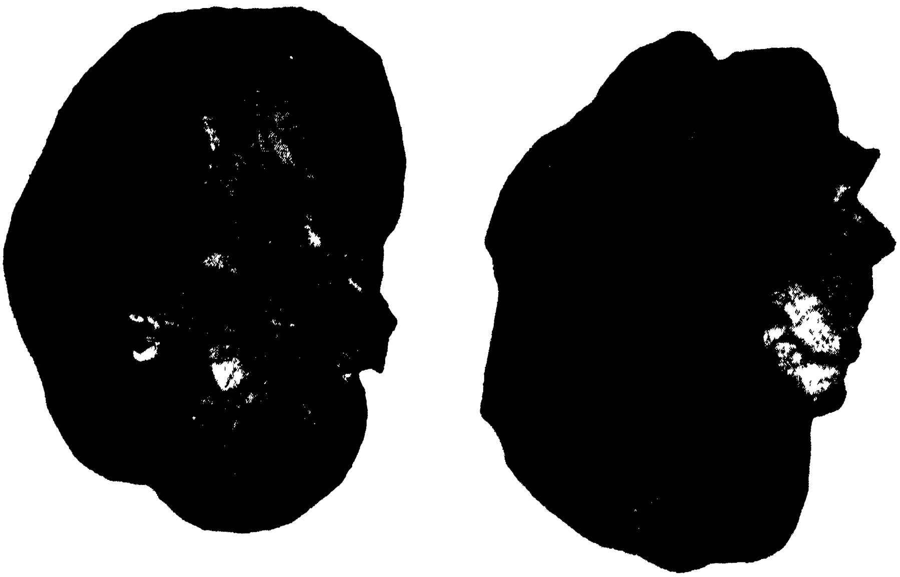

FIG. 504. *Acute Hæmorrhagic Nephritis.* Both on the surface and in the substance of the cortex are many small dark mottlings due to hæmorrhages.

Before the renal findings are given in detail, it must be again emphasised that the naked-eye appearance of the kidney frequently gives little or no indication of the nature or severity of the changes in its nephrons, and therefore, for the full understanding of the processes at work, microscopical examination is imperative.

Acute Nephritis:—

This may be regarded as the earliest, or primary, phase in nephritis. The common form of this is **glomerular** or **glomerulo-tubular** nephritis.

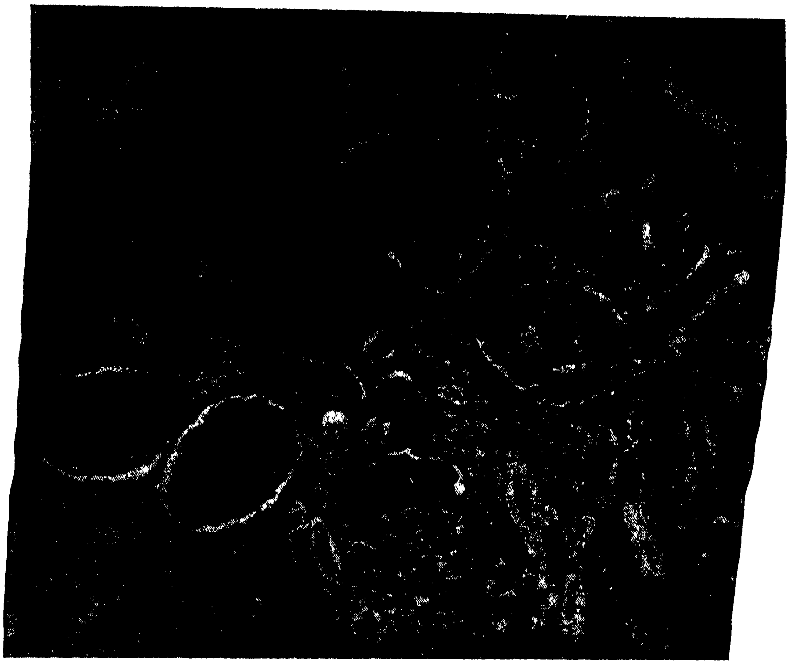

FIG. 505. *Acute Hæmorrhagic Nephritis.* Section of the same kidney as shown in Fig. 504. The glomeruli are intensely congested and blood is seen in the capsular space of several and in the lumen of several tubules. Azan. × 80.

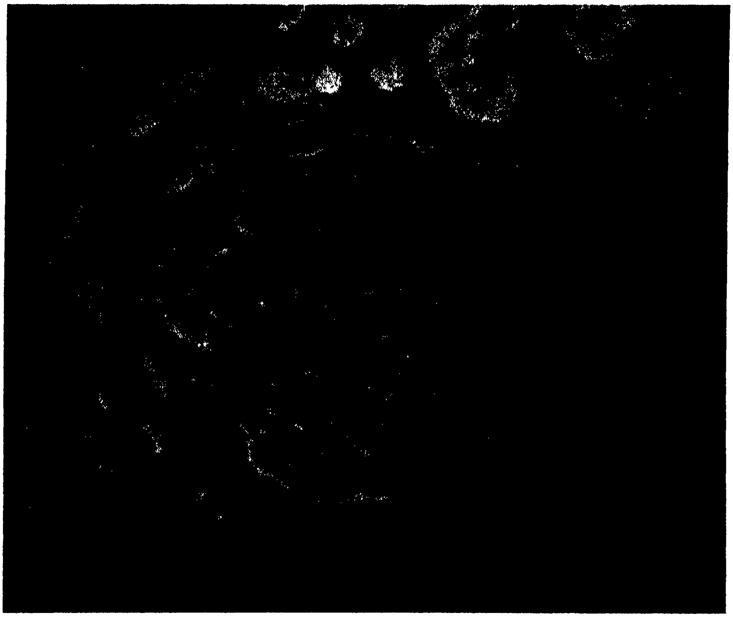

FIG. 506. ***Acute Nephritis.*** The glomerulus completely fills the **capsular space, its capillary loops are inconspicuous** and there is excess of nuclei, due to **proliferation of vascular endothelium and infiltration with leucocytes.**

The convoluted tubules show cloudy swelling, and a few of the **intertubular capillaries are engorged. Hæmatoxylin** and eosin. × **200.**

To the naked eye, the kidney is swollen and under tension within its capsule; its surface is smooth, pale grey or pink, often mottled, and may be stippled with small red spots of hæmorrhage (Fig. 504). The cut surface has a similar varied appearance in the cortex, which is swollen; the medulla is congested either throughout its extent or at the base only.

Microscopically, depending upon the exact stage at which the kidney is seen, the glomeruli are congested, or, more frequently, appear less vascular than normal; there may be some granular protein-deposit or even red corpuscles in the capsular space. The glomerular tuft shows an increase of nuclei, due mainly to proliferation of endothelium of the blood-capillaries; there may be slight hyaline swelling of the capillary wall. In some instances there is proliferation of the cells lining Bowman's capsule, though this is more a feature of the subacute condition. Polymorph-infiltration of the glomerular tuft may be found (Figs. 505 and 506).

The **convoluted tubules** are swollen and show all changes from cloudy swelling to necrosis, depending on the cause of the lesion. In acute nephritis due to chemical poisons, the tubular changes are the prominent feature, and there may be early calcification of the necrotic cells (*see also* p. 879, Nephrosis). Hæmorrhage may be seen in the form of groups of red corpuscles or blood-casts within the tubules. In some cases there is distension of tubules with granular or cellular debris and casts. The interstitial tissue as a rule shows no obvious change, or there may be slight œdema, indicated by a separation of its elements. In a rare form of **acute interstitial nephritis,** seen in some cases of scarlet fever, the characteristic feature is an intense inflammatory infiltration of the interstitial tissue with fluid and leucocytes, mainly polymorph in type.

The functional effects of acute nephritis depend upon the severity of the lesion. There is, at first, diminution, or even suppression, of urine, with the presence of albumin and casts, hyaline, granular or epithelial; blood is frequently present. There is general œdema, and, in some cases, raised blood-pressure with hydræmia (increase of fluid of blood). In a favourable case, the urine-excretion increases, albumin, blood and casts disappear, the œdema subsides, and normal function is resumed. In such cases, no traces of the damage may remain in the kidney, or at most a few glomeruli may eventually become fibrosed and disappear.

In cases of greater severity, there is a continuation of the symptoms, merging into the second or subacute stage of nephritis. Death from renal failure in the acute stage, directly due to the renal lesion, is rare.

Subacute Nephritis :—

This is an unsatisfactory term, as the cases that come under it tend to progress insidiously into a more chronic phase. Also, as previously stated, this subacute stage may be a continuation from a previous acute attack, or, the acute attack may have passed unnoticed clinically, and symptoms due to the subacute stage appear as the first clinical disturbance.

Subacute nephritis is now often referred to as the "second stage" in the nephritic process and passes under a variety of names such as "subacute diffuse nephritis," "chronic parenchymatous nephritis," "large white kidney," and some forms are known as " tubular nephritis " or " nephrosis " (*see* later, p. 879).

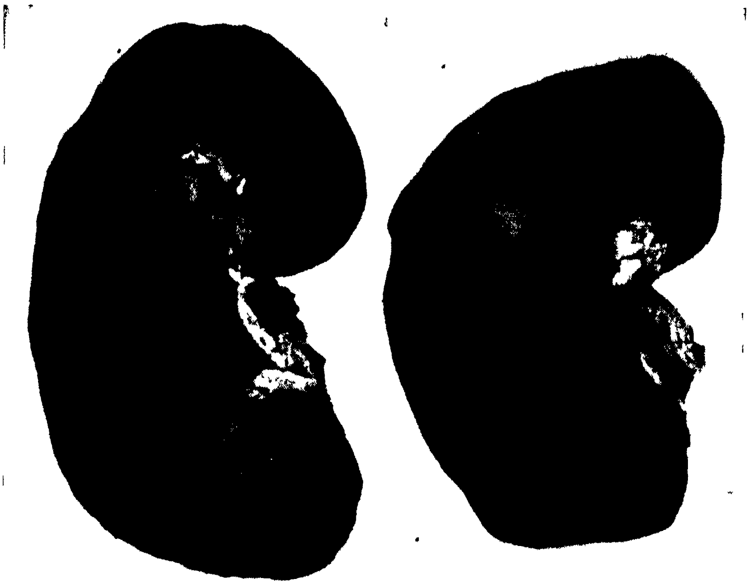

FIG. 507. *Subacute Nephritis.* Showing the appearances of the kidney described in the text.

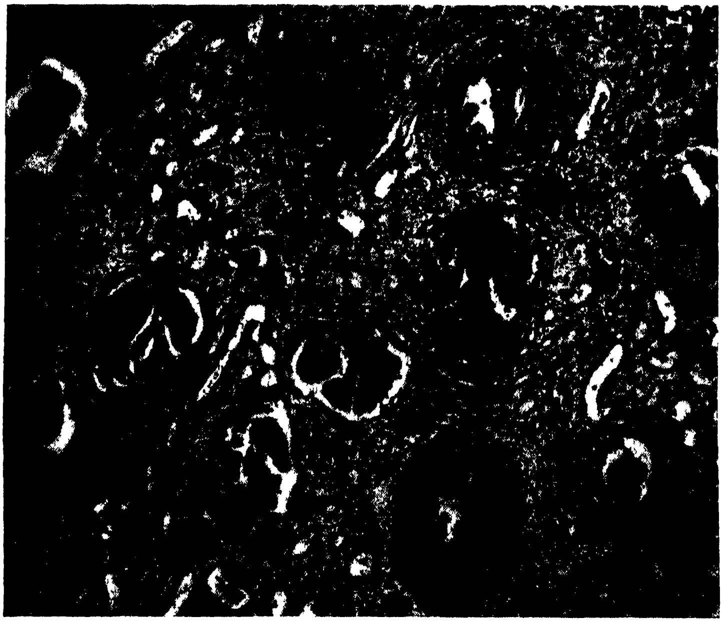

FIG. 508. *Subacute Nephritis.* Section of specimen illustrated above. All the glomeruli are affected in varying degree : a few becoming small and shrunken, the majority about normal size but showing proliferation of the cells of the glomerular capsule giving the appearance of " crescents." Adhesions between glomerular tufts and crescents are seen. The tubules vary in size, a few are small and atrophied, the majority dilated. There is œdema of the interstitial tissue causing a separation of the tubules. Hæmatoxylin and eosin. × 70.

In the form which has developed from a previous acute glomerular phase, the changes are as follows : The kidney is of normal size or slightly enlarged. Its capsule strips easily, leaving a smooth, pale pink or yellowish-white surface, sometimes mottled, sometimes marked by small red flecks of hæmorrhage. The cut surface shows the same variety of pallor, mottling or small hæmorrhages. Not infrequently, only slight pallor is noticeable and the naked-eye appearance gives little or no indication of the microscopical changes (Fig. 507).

Microscopically, the **glomeruli** show an exaggeration of the changes described in the acute phase. There is swelling of the vascular endothelium of the glomerular capillaries, and, between these cells, fine threads of reticulum can be seen by suitable staining, such as by the Azan-method or by Mallory's stain. There is often thickening of the basement-membrane of the capillaries and, according to MacCallum (1934 and 1936), there is first exudation and later proliferation of cells and fibrils between the capillaries. The net result is a varying amount of occlusion of the capillary-loops of the glomerulus. When these glomerular changes predominate, the condition is sometimes defined as " intra-glomerular " nephritis. Along with such changes there is proliferation of the lining-cells of Bowman's capsule, forming layers—sometimes in the form of " crescents "— which may extend so as to unite with the glomerular capsule partially or completely, and thus cause partial or entire obliteration of the space around the glomerulus. Between the proliferated layers, fine fibrillæ of reticulum are formed. When this capsular proliferation is the predominant lesion, the condition is described as " extra-glomerular," or " extra-capillary," nephritis. This capsular change and the adhesions interfere

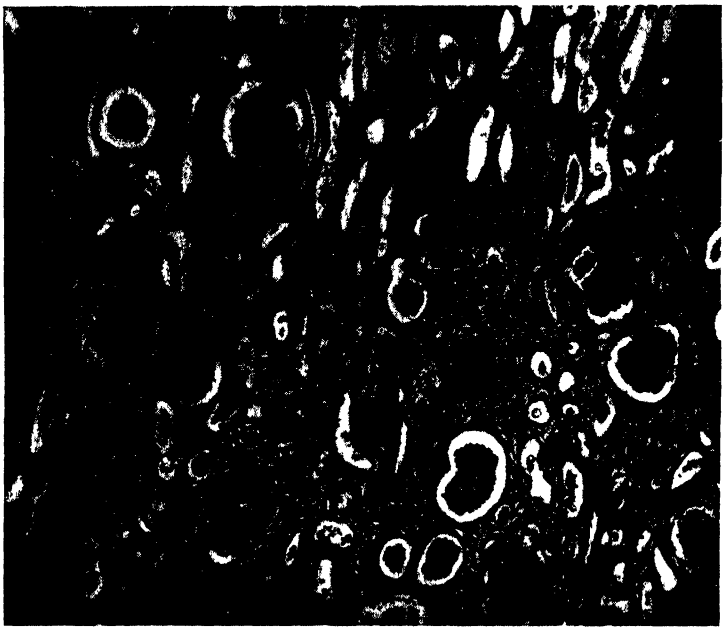

FIG. 509. *Subacute Nephritis.* Another example showing more advanced changes than those seen in Fig. 508. A number of glomeruli are fibrosed and becoming shrunken. There is definite increase of the interstitial tissue. Tubules are dilated and many contain casts. Mallory's stain. × 65.

with the function of the glomerulus as a filter. There may be fatty change demonstrable both in the glomerular endothelium and in the cells lining the capsule. In some cases, hæmorrhages into the capsular space are seen, and the blood passes down into the tubules, where it is always more obvious and gives

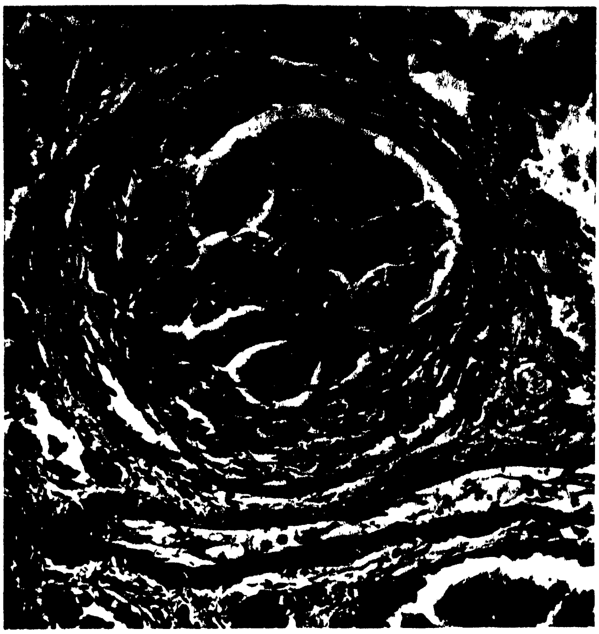

Fig. 510. *Subacute Nephritis.* Glomerulus showing lobulation of tuft, proliferation of cells lining Bowman's capsule, and progressive obliteration of its lumen. Van Gieson's method. × 200.

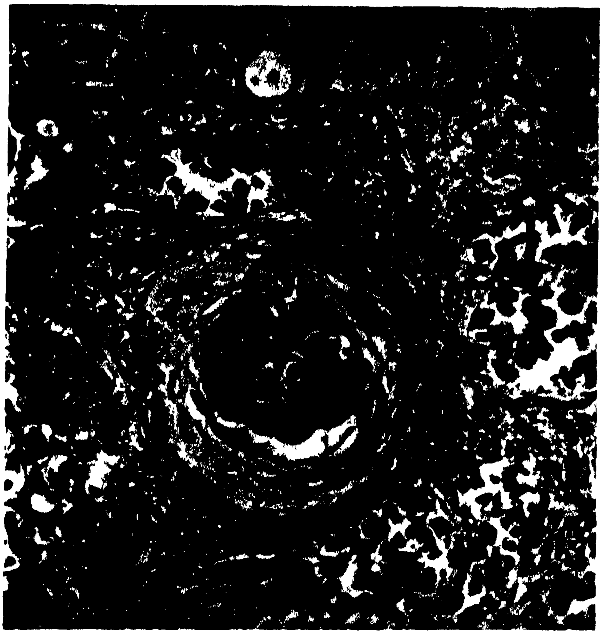

Fig. 511. *Subacute Diffuse Nephritis.* Glomerulus showing more advanced changes—adhesion to the tuft of the layers of proliferated cells lining the lumen, with obliteration of the lumen, and progressive fibrous atrophy of the tuft. × 200.

rise to the flecks seen in the naked-eye examination. All the glomeruli are affected, though not all in equal degree ; it is therefore a **diffuse** type of lesion.

FIG. 512. *Chronic Nephritis.* The kidney shows the changes described in the text.

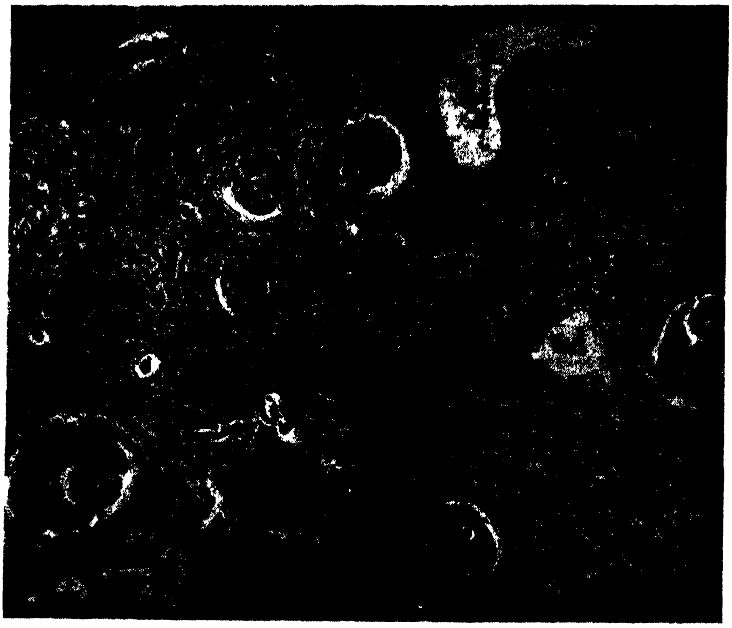

FIG. 513. *Chronic Nephritis.* A section from the kidney shown in Fig. 512. The glomeruli are closer together than normal owing to atrophy of the intervening tubules, and the majority of the tufts are small and completely fibrosed. The tubules are reduced in number and many are small and atrophic ; a few are dilated and contain casts. The interstitial tissue is increased and fibrous. Hæmatoxylin and eosin. × 70.

The **tubules** show varying degrees of degenerative changes, cloudy swelling, hyaline droplets, fatty and lipoid deposits. Often they are dilated, and contain hyaline, granular or cellular debris, or even blood. Such contents are passed in the urine during life as "casts" having the same varied characters. As yet there are but slight atrophic changes, and there may be proliferative changes in the cells of the convoluted tubules. The **blood-vessels** may show no obvious change, or there may be slight hyaline thickening of the afferent vessels to the glomeruli. The **interstitial tissue** is frequently œdematous and there may be a slight increase of its reticulum (Fig. 509).

The functional effects of these changes are albuminuria due to leakage from the glomeruli, blood in variable amount in the urine also from glomerular damage, and casts (p. 859) from the tubular changes, as noted. There is usually general œdema (*see* later, pp. 880–1) and some degree of anæmia. In the blood there is no nitrogen-retention, but there is excess of cholesterol (*see also* under **Nephrosis,** p. 879).

The termination is frequently death from some intercurrent infection, such as pericarditis, peritonitis, pleurisy or pneumonia. The symptoms may, however, abate and apparent recovery ensue, although albumin and a few red corpuscles are usually still to be found in the urine. The case becomes latent, and, sooner or later, symptoms recur, and it passes into the chronic or third stage of the disease.

Chronic Nephritis :—

Synonyms — "chronic diffuse nephritis," "chronic glomerulo-tubular nephritis," "chronic interstitial nephritis," "secondary granular contracted kidney," "small white kidney." All these terms are merely descriptions of certain of the naked-eye or microscopical appearances. The actual sequence of events can be assumed only from the study of many cases coming for examination at various stages in the process.

Some forms of chronic nephritis are chronic from the outset, as far as clinical records go. When first examined, they show all the findings associated with a chronic renal lesion. The earlier stages may have been overlooked ; more probably they are examples of repeated focal lesions, no one of which has been sufficient to cause symptoms, but each one of which has destroyed a limited number of nephrons, until a stage has been reached when the surviving kidney-tissue is inadequate to carry on proper excretory functions. Vascular hypertension is a complication at this stage, and in any given instance of this type it is often a difficult problem to decide whether the disease has been primarily vascular or primarily renal.

In the type of case following on a previous acute or subacute lesion, the changes are easier to follow. The **naked-eye appearances** give some clue as to the finer changes. The kidney is reduced in size, the capsule may strip cleanly or show adhesions in places. The surface is finely granular, pink, pale-yellow or mottled, and an occasional small hæmorrhage may be seen. There may be a few small cysts. The cut surface shows a reduction in the depth of the cortex, with some irregularity of the vascular markings and of the bases of the pyramids ; it also is mottled yellow or pink. Some kidneys show, in addition, cream-coloured markings and streaks due to lipoid deposits, usually near the boundary zone ("myelin-kidney"). The pyramids may be reduced in size also, but relatively less so than the cortex. The larger arteries may appear normal or be slightly rigid from arteriosclerotic changes, but in lesser degree than in the typical primary arteriosclerotic kidney (Fig. 515).

The **microscopical changes** described under Subacute Nephritis proceed a stage further (Fig. 513). Many **glomeruli** become functionless, due to occlusion of their capillaries and fibrosis within the tuft, or they may be occluded by the capsular proliferation and fibrosis, or by the blood or fibrin within the capsular space becoming fibrosed. Such glomeruli eventually show as fibrous knots. Others appear larger than normal; these have been less damaged and have been carrying on such function as was left, but even these frequently show scars of limited damage, and fatty changes may be found in their vessels.

The **tubules** supplied by the fibrosed glomeruli suffer from loss of function, no fluid being passed to them, or from loss of blood-supply owing to the obliteration of the vascular tuft of the glomerulus; these, therefore, atrophy and may be seen as narrow tubules lined by small, flat cells, or they may completely disappear. Here and there are unaffected, and even hypertrophied, tubules, which have escaped either because they were part of the nephrons with still active glomeruli, or because they had an extra blood-supply from the little vessel of Ludwig, the branch derived from some afferent vessels before they reach their glomeruli, and which goes direct to the intertubular plexus (Fig. 498, p. 856). Fatty droplets may be seen in the cells of these tubules as well as in those of some of the atrophying tubules. Small **cysts** may be formed from distended tubules. Dilated and atrophied tubules may show "colloid" material within them in some cases.

The **interstitial tissue** is increased and fibrosed (hence the term "chronic interstitial nephritis"), and the atrophic tubules are separated by it. There may also be deposits in it of neutral fat or cholesterol-esters. In places there may be found small collections of lymphocytes.

The **blood-vessels** show arteriosclerotic changes. The small afferent glomerular vessels are hyaline and the larger arterioles and arteries show a varying degree of arteriosclerosis, though not, as a rule, to the same extent as in the primary arteriosclerotic type of kidney.

Evidence of the **functional effects** of such changes are found especially in the modifications in the urinary excretion. There is an increase in the volume of the urine, but only in its watery content; the specific gravity is low (*e.g.*, 1·010) owing to a reduction in solids from lack of concentrating power of the atrophic tubules. Casts are few and usually of the hyaline variety. Albumin is present in traces only. The excretion of urea, uric acid and creatinine is reduced, due largely to the inability to concentrate urea, etc. In the blood, these substances are increased, and the total non-protein nitrogen may reach high figures, *e.g.*, 200 mgr. or more per 100 c.cm. Owing to retention of acid-products there may be an acidosis. The blood-pressure is raised.

Death may occur from renal failure—uræmia—owing to accumulation of waste-products; or, it may occur from heart-failure or cerebral hæmorrhage, though such terminations are commoner in primary hypertension. In some cases of chronic nephritis, and also in some of arteriosclerotic renal damage, there may be extensive ulceration of the lower part of the ileum and colon, so-called "**uræmic ulceration.**" The exact nature of this is still not clear, but in those examples we have examined there appeared to be intense venous congestion of the intestinal mucosa as the primary factor, leading to thrombosis and hæmorrhage, which was followed by ulceration of the overlying mucosa.

In all instances of chronic nephritis, a superadded acute change may occur in the damaged kidney and precipitate a fatal result, there being no reserve of tissue to carry on function.

Nephrosis :—

In the foregoing account of renal lesions, the term " nephrosis " has appeared on several occasions. It is necessary to define this further, as it is a term now in common use, especially among clinicians ; pathologists, on the other hand, find difficulty in defining " nephrosis " as a separate entity. It is a change in degree rather than in kind.

The term " nephrosis " is applied clinically to a type of disease characterised by persistent œdema, albuminuria, high blood-cholesterol, but no nitrogen-retention ; and it is said to occur without any obvious antecedent acute phase and to continue for a long period, even years. Recovery may occur, or death from some intercurrent disease. All these findings can equally well be obtained in what is recognised and admitted to be a subacute nephritis of primary glomerular type, and the term " **nephrotic syndrome** " is used to include those features given above, whether they are associated with what is termed a pure example of nephrosis (or " lipoid nephrosis "), or with an admitted subacute nephritis.

Volhard and Fahr (1914) maintain that the pure " lipoid nephrosis " should be regarded as a separate entity, degenerative in nature, but Fahr (1918) reported only eight fatal cases in twelve years, and, in his account,[1] he describes and figures glomerular changes, minor in degree it is true, but comparable to the minor changes in glomeruli in glomerulo-nephritis.

Pathologically, the term " nephrosis " may be applied to the tubular changes seen in various renal conditions. From the action of many chemical poisons : in the renal changes of eclampsia and other " toxæmias of pregnancy " : in the acute infections, *e.g.*, pneumonia, many septicæmias and fevers, there are changes in the tubules ranging from mild cloudy swelling (*e.g.*, in a febrile state) to definite necrosis (*e.g.*, in poisoning by corrosive sublimate). In all these cases, there may be no demonstrable lesion in the glomeruli and yet we judge, from the clinical findings of albuminuria, that a glomerular leak has been present. In the milder cases of subacute nephritis, the glomerular changes may be minimal, and yet the tubular changes maximal, by histological standards. Whatever material reaches the lumina of the tubules must first have passed through the glomerular capillaries, except where an occasional and relatively unimportant vessel of Ludwig is present to short-circuit the glomerulus (*see* Fig. 498, Diagram, p. 856). Therefore the glomeruli filter off, and are exposed to, the same damaging agents,

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[1] In Henke and Lubarsch, " *Handbuch der speziallen pathologischen Anatomie und Histologie,*" 925, **6**, 1.

e.g., toxins, as the tubules. In the tubules, great concentration of urine with reabsorption of water and other substances occurs over a relatively long extent of tubule; such tubules are thus exposed to a greater amount and presumably a greater concentration of toxin or poison. It is, therefore, natural that, if the glomerulus is not damaged by the toxin or poison sufficiently to prohibit the passage of the latter onwards, the tubules will receive a heavier insult. It is just in those cases of less severe glomerular damage that tubular changes of a "degenerative" character are most marked. As the glomerular lesion increases, filtration diminishes and the tubule atrophies.

In the subacute phase of nephritis where the "nephrotic syndrome" predominates, the tubules show marked loading with doubly refractile lipoid due to accumulation in them of cholesterol-esters, and such lipoid may also appear in the urine. In the blood, there is a pronounced hypercholesterolæmia (600 to 1,000 mgr. per 100 c.cm.), and it would appear as if the leaking glomeruli permitted not only protein but cholesterol-ester to pass, the latter being partly reabsorbed by the convoluted tubules. The appearance of lipoid is in these cases, therefore, not necessarily a degenerative phenomenon.

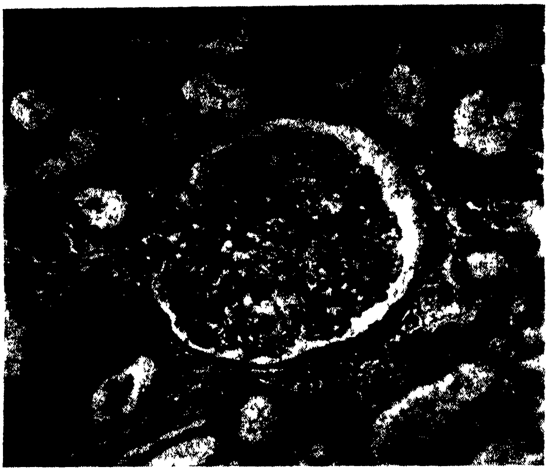

FIG. 514. *Kidney from case of "Nephrosis."* There is little obvious glomerular change, at most a slight thickening of the glomerular reticulum between capillaries. The tubules are distended with granular content and a hyaline cast is visible in one. The interstitial tissue is slightly œdematous and some intertubular capillaries are engorged (red corpuscles appear black). Stained by Mallory's method. × 165.

The cause of the hypercholesterolæmia in the nephrotic syndrome is not known. It is due probably to causes outside the kidney, for it may occur apart from renal disease, *e.g.*, in pregnancy and in starvation.

Apart from what may be termed the "acute toxic" and "chemical nephroses"—cloudy swelling, etc.—due to toxæmias and poisons, three varieties of special nephrosis or "lipoid nephrosis" may be recognised, if we accept the primary lipoid nephrosis of Volhard and Fahr as a separate entity. They are: (1) Primary lipoid nephrosis, (2) the nephrotic syndrome of subacute nephritis, and (3) the amyloid kidney. The last has been described (pp. 210–11 and 858) as a degenerative lesion primarily affecting vessels. In all of these there is usually a large, pale kidney, with pronounced albuminuria and œdema. The tubular changes are prominent histologically and the glomerular changes vary with the extent or type of disease (Fig. 513).

Œdema in Renal Disease (pp. 180–1). In the acute phase of nephritis, œdema is present and is associated with an oliguria, raised blood-pressure and increased content of plasma within the blood-vessels. The œdema-fluid is relatively rich in protein. The œdema is due probably in part to the damaging effect on the capillaries of the body by the cause (*e.g.*, streptococcal toxin) of the nephritis, together with the increased blood-volume and -pressure and the reduced elimination of fluid by the kidney.

In the subacute phase, the œdema-fluid contains less protein. Its presence in the tissues appears to be due chiefly to the alteration of plasma osmotic pressure from the protein-loss through the kidney. This loss is mainly of the albumin-fraction of plasma-protein owing to its smaller molecular size, while the amount of the globulin remains only slightly or not at all reduced. The normal ratio of the amounts of albumin and globulin in blood-plasma ranges from 2 : 1 to 2 : 1·2 approximately ; owing to loss of albumin this ratio may be upset. Loss of plasma-albumin means less osmotic pressure being exerted within the vessel to retain fluid, which consequently passes out into the tissues, carrying with it sodium chloride to maintain equilibrium of salt within and without the vessel. Sodium-chloride retention is not a cause of œdema, as salt is easily excreted by even a damaged kidney, and is retained only in amounts sufficient for equilibrium as stated.

When, owing to fibrosis of glomeruli in the chronic stage of nephritis, albumin ceases to escape, the œdema passes off, the plasma osmotic balance being now restored. Although this explanation of the œdema seems to fit many cases, there are occasional anomalies such as disappearance of œdema without restoration of the albumin-globulin ratio ; and, conversely, there may be œdema with little disturbance of ratio. Other factors, such as a sufficiency of salt and of water, are required to make the retention of fluid possible ; and the relation of glomerular filtration to tubular reabsorption is important. Excess of reabsorption would mean oliguria, and a retention of fluid in the body ; deficient reabsorption would give a more dilute urine and polyuria—provided sufficient glomeruli were available. For a detailed discussion on this aspect of renal function and its relation to renal disease, see J. Shaw Dunn's articles on the subject.[1]

The Arteriosclerotic Kidney. Synonyms—" Small red kidney," " granular contracted kidney," " nephrosclerosis."

Two forms of this may be recognised : (*a*) the form associated with arteriosclerotic changes in some of the larger renal arteries and without necessarily any raised blood-pressure. The kidney in this form shows a few coarse atrophic depressions on its surface, corresponding to the few medium-sized cortical branches which have become sclerosed and obliterated. This form is often found as a senile change. It is of little importance clinically or pathologically, as sufficient kidney-tissue is left to carry on function.

(*b*) The second form is associated with increased blood-pressure and is sometimes called " the kidney of essential hypertension " (hyperpiesis). In this it is the smaller branches of the renal arterial tree that are involved, especially the arterioles—hence the term " arteriolosclerotic kidney."

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[1] *Brit Med. Jour.*, 1933, *ii*, 477 and *Lancet*, 1934, *i*, 1107, and also *Proc. Roy. Philos. Soc.*, Glasgow, 1940, **64**, 106.

Of this form two varieties are recognised—the "benign" and the "malignant," though they may be combined. These terms refer to the duration and severity of the lesions.

This form of nephrosclerosis is associated with a persistent high blood-pressure, to the extent of 180 to 250, or even more, mm. of Hg, and the renal lesions are, as it were, only an incident in the general arteriosclerosis.

Structural Changes :—These depend on the degree and extent of the vascular lesions and whether or not the patient has succumbed to the renal damage or to the effects of the hypertension on other systems. **Naked-eye** : In the minor degrees of renal vascular sclerosis, there may be little deviation from normal or only a slight granularity of surface and reduction in size. In a pronounced case, the kidney is reduced in size by a third or a half, the capsule tends to be adherent to the surface, which is granular or undulating. On section, the cut surface shows reduction of the cortex. The larger renal vessels and those in the boundary-zone may appear rigid and thickened. This type of kidney is sometimes called the " small red kidney," but the " redness " is a variable feature due to congestion which depends largely on the mode of death, *e.g.*, heart-failure tending to its production. There may be a few small cysts at the surface or in the substance. The gross appearances, therefore, closely resemble those of the chronic nephritis of glomerulo-tubular origin, and it is often impossible to distinguish the two by naked-eye examination alone (Fig. 515).

FIG. 515. *Arteriosclerotic Kidney* (" hypertensive kidney "). As described in the text: the organ is small, its surface granular, its substance reduced—indicated on the cut surface by the narrowed cortex.

Microscopically (Fig. 516) :—The most pronounced changes are seen in the arteries and arterioles. The larger arteries show the changes of diffuse arteriosclerosis—a diffuse intimal thickening, with increase in amount of elastic tissue, medial hypertrophy and fibrosis. The smaller vessels, such as the intertubular arteries and afferent arterioles, show relatively more sclerosis, their walls being thickened, fibrous or hyaline, and the lumen much reduced. On cross-section, the afferent vessel may appear like a piece of rubber pressure-tubing, the proportion of lumen to wall being correspondingly altered. The lumen may eventually even become occluded. The corresponding glomeruli show hyaline thickening affecting them from their afferent vessels to the walls of their capillaries. As the vessels gradually become narrowed, the glomeruli shrink, until finally they appear as mere fibrous knots. There is usually also fibrous thickening of the glomerular capsules. This change is patchy, the vessels most affected being those associated with fibrosed atrophic glomeruli, and, as a result, the corresponding tubules atrophy. It is the shrinkage of such units that causes the depressions on the surface. Other units, or groups of units, may be little affected, and, indeed, their glomeruli may even appear larger than normal from compensatory hypertrophy.

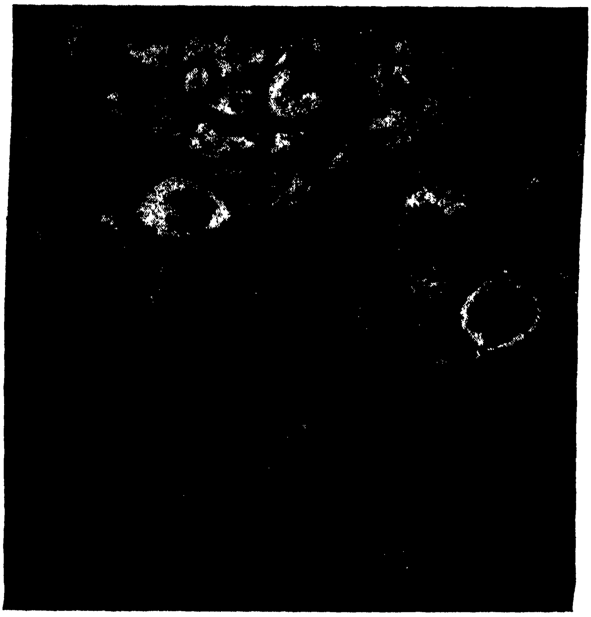


FIG. 516. *Arteriosclerotic (hypertensive) Kidney.* In one area (near centre of figure a group of several fibrosed and shrunken glomeruli (dark in appearance) are seen closer together than normal and surrounded by atrophic tubules and condensed interstitial tissue. Several afferent arterioles show great sclerosis of their walls. Adjacent to this area is a group of tubules all somewhat dilated, but exhibiting no atrophic change and having no interstitial increase between them.
Mallory's stain. × 60.

In the so-called "malignant" form of hypertensive kidney, the above appearances are found, but, in addition, small points of hæmorrhage may be seen with the naked eye ; and, microscopically, the small sclerosed afferent vessels may become necrotic and thrombosed or even ruptured (Fig. 517, B). Thrombosis and hæmorrhage may also be seen in some glomeruli. This more extensive and more acute damage may lead to greater and more rapid loss of kidney-units and precipitate renal failure. The victims of the " malignant " nephrosclerosis, therefore, frequently die of renal failure in the same way as do those suffering from the chronic nephritic kidney. In the case of the " benign " hypertension, a fatal result is much more frequent from failure of the heart under the strain of the high blood-pressure, or from rupture of a cerebral vessel and fatal apoplexy. In those cases in which the heart begins to give way, there may be a terminal failure of renal excretion, as the arteriosclerotic kidney is capable of excretion only so long as the blood-pressure is kept sufficiently high.

As already mentioned under Ætiology of Nephritis (p. 867), the exact nature of the causal factors of the hypertension is still uncertain.

Eye-lesions are of frequent occurrence in chronic nephritis and in arteriosclerosis with high blood-pressure. The arteries in the retina have thickened walls which appear white, "like silver-wire," on examination of the retina with the ophthalmoscope. Hæmorrhages, old and recent, may also be seen, and, if there is cerebral œdema, there may be swelling of the disc (" papillœdema ").

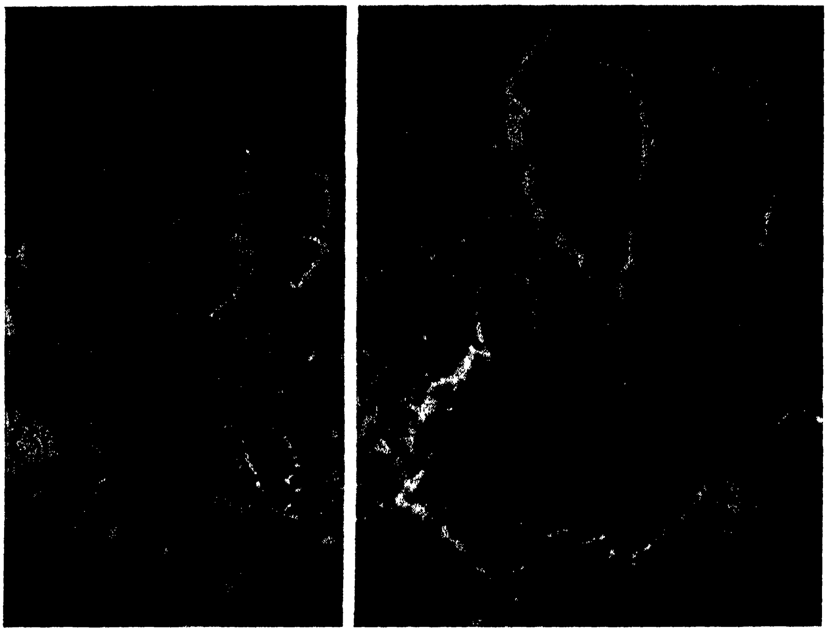


FIG. 517. *Arteriosclerotic (hypertensive) Kidney.* Two glomeruli from different areas of the same kidney. (Red blood-corpuscles appear black.) × 220.

A. " Benign " variety. The glomerulus is small, its vascular loops reduced in size, retracted from the capsule and showing hyaline thickening of their capillary walls. The afferent arteriole has a thick hyaline wall and reduced lumen.

B. " Malignant " variety. The afferent vessel is thrombosed and its wall necrotic; hæmorrhage has occurred into adjacent tubules and interstitial tissue. The glomerular capillaries are engorged with blood.

Trench-Nephritis. In the War of 1914-1918, and also in the American Civil War, during the prolonged periods of trench fighting, large numbers of cases of acute nephritis occurred. After eliminating the various forms of acute and chronic nephritis equally typical of civil life, a large proportion of cases remained, characterised by severe **dropsy** (which usually rapidly subsided), diminution or even temporary suppression of the urinary secretion, pronounced **albuminuria,** often persisting for a considerable time, **hæmaturia,** the presence of **renal casts,** especially of granular and hyaline type, with uræmic symptoms.

In comparison with the severity of the clinical symptoms, the mortality was extraordinarily low and many cases recovered completely. The type of nephritis was acute or subacute glomerular,, as already described under those headings. The ætiology remained undetermined, though some evidence was brought forward to suggest that it might be due to a filter-passing virus.

SPECIFIC (mostly CHRONIC INFECTIVE) DISEASES of the KIDNEY :—

(*a*) **TUBERCULOSIS of the KIDNEY** (pp. 72–5). This may be part of a general acute or chronic tuberculosis, but, in some cases, the disease is more or less limited to the genito-urinary system.

In **General Acute Miliary Tuberculosis,** small tubercles may be seen : often scanty, occasionally in groups or clusters.

In many cases of **pulmonary tuberculosis,** tubercle bacilli have been found in the urine, and histological examination of kidneys from such cases may reveal a number of minute foci in glomeruli or amongst tubules. There may be no naked-eye evidence of these, but in other cases larger tuberculous foci are found. In the so-called " primary tuberculosis " of the kidney, the bacilli have probably reached the kidney by the blood-stream from some other focus, such as lung or bone, though the lesion in these areas may have been overlooked, or have become quiescent.

Infection may reach the kidney by the ureter, as illustrated by the following case which was one of tuberculosis involving the left iliac bone. On that side were two ureters with separate pelves in the kidney above and proceeding separately to the bladder. One ureter was involved in the tuberculous process and was thickened and caseous throughout its whole extent from bladder to its pelvis. This pelvis and the portion of kidney served by it was extensively caseous. The other ureter was healthy and its portion of kidney unaffected. The opposite, right, kidney—which had only one ureter—was quite unaffected. In this case, spread had undoubtedly been by the ureter and was limited to one of two. The other acted as a control in this somewhat unusual human " experiment " (Fig. 41, p. 73).

Results. Most commonly, genito-urinary tuberculosis is a steadily progressive disease leading to a fatal termination. In a few instances, however, the process is arrested and the caseous material becomes inspissated and perhaps calcified, and surrounded by dense fibrous tissue corresponding with the capsule of the organ. Such instances of " healed " tuberculosis of the kidney may sometimes be found in the bodies of even elderly persons, in whom the presence of genito-urinary tuberculosis had been unsuspected during life.

(*b*) **ACTINOMYCOSIS** (p. 91). This disease may affect the kidney as part of a generalised spread from some focus of disease in connection with the intestine, appendix, or elsewhere, or the condition may spread to the organ by direct continuity. In the former case, multiple small nodules, tending to soften and form small abscesses, are found. A perinephric abscess may supervene. The condition is rare.

(*c*) **SYPHILIS** (p. 88). Apart from amyloid degeneration, the kidney rarely shows any definite syphilitic lesions, but, when these are found, they are of the same character as in other organs. In the congenital syphilitic infant, spirochætes may sometimes be demonstrated without necessarily any structural alteration in the organ. **Gummata** (Fig. 518) or their scars are occasionally seen and the latter may closely resemble those of old infarcts. Vascular lesions of the renal arteries may occur. A rare form of interstitial nephritis is described by Rich (1932) as occurring in cases of syphilis.

Amyloid degeneration is one of the commonest evidences of the disease, and is often associated with interstitial changes, and the formation of cysts. In these syphilitic amyloid kidneys, the capsule is not necessarily thickened or unduly adherent, and the surface of the organ is usually granular, the elevations being larger and more irregular than those seen in granular contracted kidney. The uneven surface frequently presents an undulating character. Unless other causes are also present, these changes in the kidney are not necessarily—and, in fact, are seldom—accompanied by hypertrophy of the left ventricle. (For a further account of amyloid disease of the kidney, *see also* pp. 210–11 and 858.)

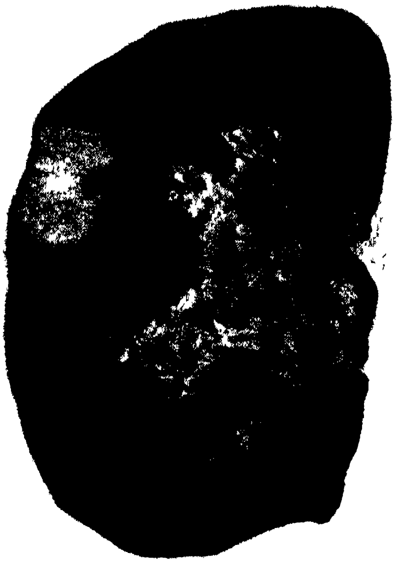


FIG. 518. *Syphilitic Gumma of Kidney.* The pale somewhat wedge-shaped area resembles an infarct but microscopically it proved to be syphilitic. Gummata were present elsewhere in the body.

(*d*) **THE LEUKÆMIAS.** Especially in the "**lymphatic**" forms, characteristic changes are found in the kidney. The interstitial connective-tissue framework of the organ, especially around the vessels, is infiltrated with cells of the leucocyte-series, the nature of which varies with the type of the disease—myelocytes and immature polymorphonuclear cells being present in the myelogenous, the smaller or larger lymphocyte-like cells in the lymphatic, variety (pp. 631 and 634, and Fig. 500, p. 861).

URINARY CALCULI—NEPHROLITHIASIS

These are composed of certain normal or abnormal constituents of the urinary secretion which, either because of their excessive amount, or from precipitation owing to the occurrence of certain chemical changes—*e.g.*, those found in decomposition of the urine—crystallise out, or are deposited in amorphous form. Such calculi (Fig. 519) may be composed of one, or, in many cases, of a mixture of two or more, of the following substances: **uric acid, urates, calcium oxalate, phosphates,** and, more rarely, **calcium carbonate, cystin, xanthin,** or **cholesterol.** In the calculus, these substances are bound together by an organic matrix, usually altered mucus, fibrin or cell-debris; and the calculi themselves may have a laminated, and frequently also a radially striate, structure. The "nucleus" of a calculus is usually composed of urates or uric acid or, in some cases, may consist of a foreign body. Where schistosomiasis occurs, as in Egypt and elsewhere, *Schistosoma* (*Bilharzia*) ova, or broken-off fragments of Bilharzial papillomata containing them, may form the nucleus of calculi. Inflammatory, degenerative, and necrotic processes play an important part in the production of some calculi, *e.g.*, inflammatory products become infiltrated with the various chemical substances mentioned above. On the other hand, calculi, once formed, act as foreign bodies, the irritation of which either helps to keep up a pre-existing inflammation such as a pyelitis or cystitis, or predisposes towards its occurrence.

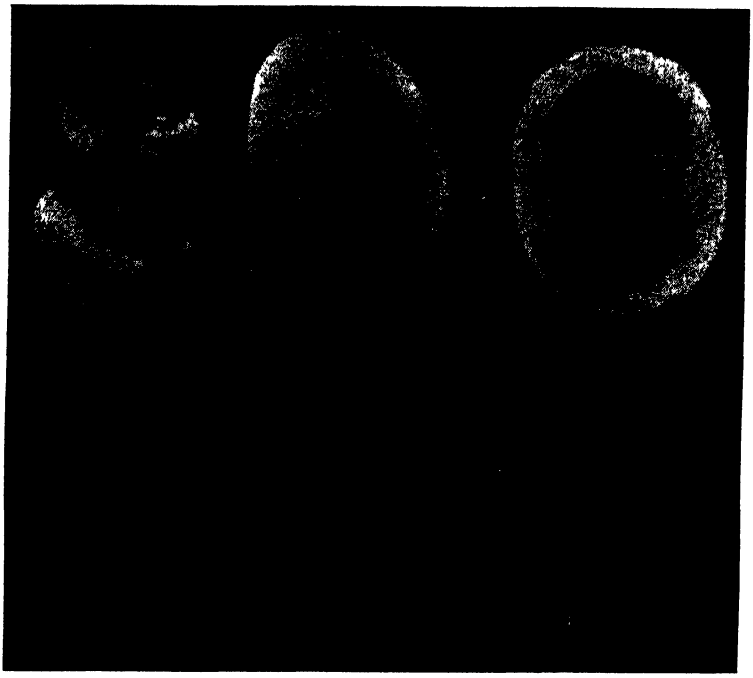


FIG. 519. *Urinary Calculi.* All show concentric lamination, the result of repeated deposition of the components of the calculi.

(A) These three calculi consist mainly of phosphates. The dark centre in the right-hand specimen is composed of uric acid.

(B) This calculus is formed mainly of uric acid.

(C) A mixed calculus with darker centre of uric acid and lighter surface layer of phosphates.

(D) An irregular calculus, with rough surface, composed of an admixture of oxalates and uric acid. (Two-thirds natural size.)

Calculi are single or multiple, and may be found in the kidney, the ureter, or the bladder. They may lie free in the bladder, or be embedded in a diverticulum, or they may be impacted at the opening of the ureter.

Uric-Acid Calculi are formed where uric acid crystallises out in consequence of excessive acidity of the urine, the acid-phosphates using up some of the bases which should, under normal circumstances, be combined with it. Uric acid may also be precipitated where it is present in excessive amount because of dietetic and other errors ; or where the watery part of the excretion is insufficient in amount to hold it in solution. Uric-acid calculi are hard in consistence, and more or less spherical or ovoid in shape. They are usually yellowish- or reddish-brown in colour, from the associated presence of urinary pigment. They are generally slowly formed, and may, if the urine becomes alkaline from decomposition, form the "nuclei" of more rapidly growing phosphatic stones.

Urate-Calculi, composed of ammonium- or of sodium- urate, are rare. They are found chiefly in infants, though they also occur in adults from ammoniacal decomposition of the urine.

Calcium-Oxalate Calculi may originate in the pelvis of the kidney, and be carried down into the bladder. They are extremely hard, and usually present a rough, nodulated or "mulberry" exterior, by reason of which they give rise to considerable irritation and hæmorrhage, and are themselves generally stained a dark-brown or brownish-black colour from the presence of blood-pigment. They frequently show an admixture with uric acid, and may form the nucleus of phosphatic concretions.

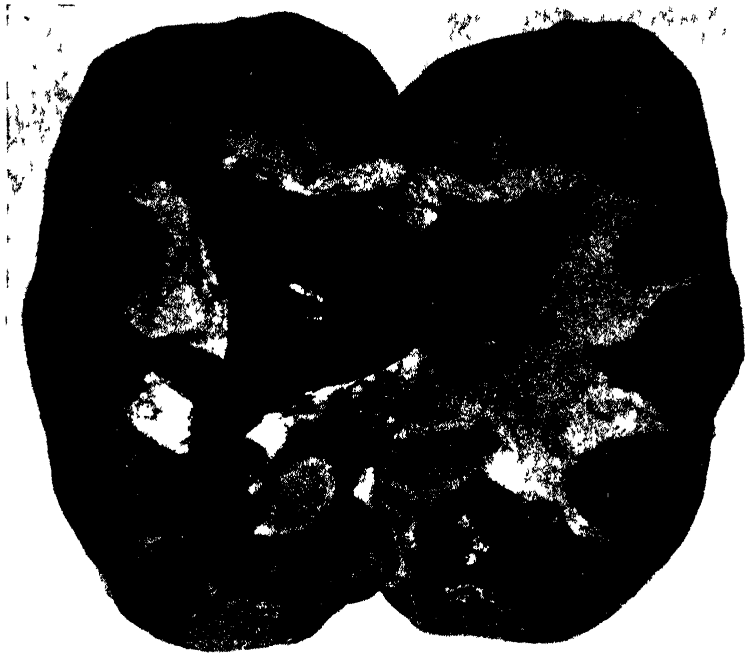


FIG. 520 *Coralline Calculus in Kidney.* There is a large calculus occupying the dilated renal pelvis and calices with many separate fragments in the latter regions. The dark colour of the main calculus is due to blood deposited on its surface. The patient was a married woman aged 63 years

Phosphate-Calculi are found especially where there is ammoniacal decomposition of the urine due to bacterial infection. They are pale and chalky in appearance, soft and friable, and are composed mainly of magnesium and calcium phosphates, usually mixed with varying quantities of calcium oxalate and ammonium urate, mucus, and urinary pigment. They are found commonly in cases of cystitis in which the urine has become alkaline from decomposition, and they frequently exhibit a "nucleus" of uric acid. They are soluble in the mineral acids without evolution of gas.

Calcium-Carbonate Calculi, though common in herbivora, are rare in man. They are often extremely hard, though soft forms are sometimes found. They readily dissolve in a mineral acid, carbon-dioxide gas being given off.

Cystin-, Xanthin-, and **Cholesterol-Calculi** are rare.

Calculi may be formed in the pelvis of the ureter or in any of its calices ; or they may originate in the renal tubules, more especially in the larger collecting tubules near their openings at the apices of the papillæ. Renal calculi may be carried downwards and become impacted in the ureter, leading to hydronephrosis (p. 890 *et seq.*) ; or, if small enough, they reach the bladder, their passage down the ureter giving rise to an attack of "renal colic." In the bladder, they can act as the nuclei around which further concretions are formed ; or, if not too large, they pass through the urethra and are found in the urine as the so-called urinary "gravel." In some instances, they partially or almost completely fill the pelvis of the ureter and its calices, forming the so-called **coralline calculus,** which may either be single (Figs. 520–1), or composed of two or more faceted constituent parts. In some instances, several or even very many small calculi are found in the pelvis, in its calices, or in the renal substance. Both kidneys may be the seat of calculus-formation, especially in the later stages of the disease, and are, therefore, more frequently found to be so affected on post-mortem examination than in surgical practice. Calculi are commonest in mid-adult life, but can occur also early in life, the phosphatic being the commonest form found in childhood.

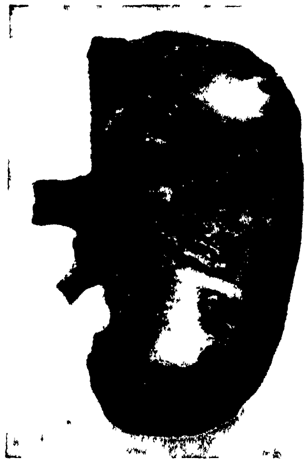


FIG. 521 *Coralline Calculus* occupying pelvis and calices of ureter, the glandular tissue of which is greatly atrophied. The central limb of the calculus has been broken off to show the bed in which it lay.

Ætiology and Results. In the kidney, various concomitant lesions may be found, either as the cause or the result of calculus-formation ; or both may be produced by some other common factor. Thus calculi may be found along with various forms of nephritis, with partial or complete **atrophy** of the kidney, or with **perinephritis.** There is often an associated **pyelitis** and **pyelonephritis,** which may, perhaps, have some causal relationship ; whilst, on the other hand, the presence of calculi may lead to these conditions, or further aggravate them if already present. In addition to such inflammatory phenomena, renal calculi are a common cause of **hæmorrhage,** and they may also, as already mentioned, become impacted in the ureter, and give rise to **renal colic** and to **hydronephrosis** or to **pyonephrosis.** If carried down into the bladder, they may, as indicated above, constitute the nuclei for further calculus-formation in that organ.

Sometimes the substances of which calculi are composed—especially uric acid, urates, or lime-salts—may be deposited in crystalline or in amorphous form, in the renal tubules, especially in the pyramids towards their apices. A deposit of lime-salts may occur in necrotic renal epithelium, *e.g.*, following poisoning by corrosive sublimate, etc.; and, similarly, " incrustation " with calcareous material may occur in the walls of the renal pelvis and ureter, the process being also probably secondary to degenerative and necrotic changes in these structures. In the same way bile-pigment may be deposited in a similar position, *e.g.*, in icterus neonatorum, and in chronic jaundice in adults.

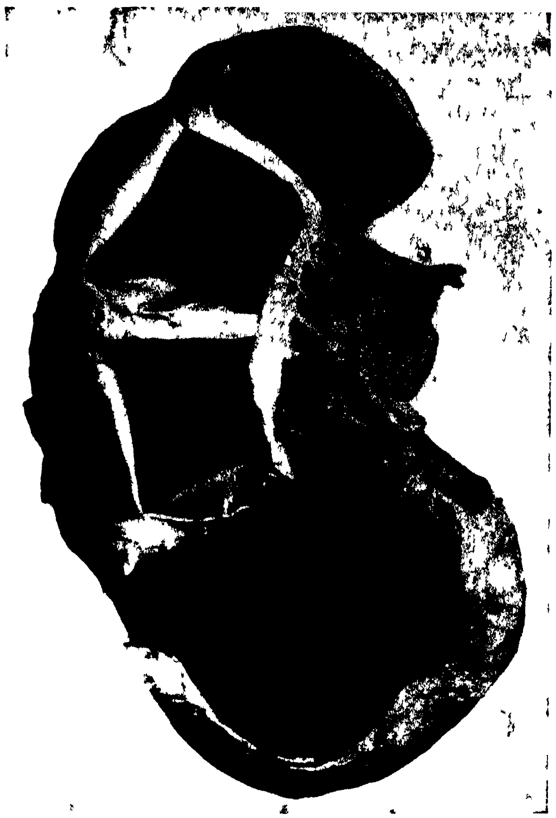


FIG. 522. *Hydronephrosis of Kidney due to obstruction of the Ureter.* The renal pelvis and infundibula or calices are enormously dilated, and the glandular tissue has completely atrophied.

Calculi may be found where there is excessive excretion of calcium as in hyperparathyroidism (p. 838).

HYDRONEPHROSIS. This is a condition of dilatation of the pelvis of the ureter and its calices. It may arise from any cause which impedes the outflow of urine from the renal pelvis. The amount of dilatation depends on the degree and rate of obstruction. Sudden complete obstruction leads to extreme distension of the pelvis and calices, but soon the pressure within the distended pelvis leads to stoppage of secretion, and, if the obstruction is not removed, the kidney will in time atrophy. More slowly-produced obstruction or intermittent obstructions lead to greater degrees of distension and dilatation with expansion of the kidney-substance which may eventually be reduced to a mere shell of atrophic renal tissue around large loculi, formed by the expanded calices. The ureter above the obstruction is also dilated.

FIG. 523. *Hydronephrosis due to Abnormal Renal Artery.* This artery enters the lower pole of the kidney and the ureter, in crossing the vessel, has become kinked and obstructed. Part of the dilated pelvis is seen above the artery and the kidney has been opened to show the continuation of the pelvis and the dilated calices.

Histologically, in pronounced hydronephrosis, there is a loss of the regular vertical lines of collecting tubules which are represented by horizontal tubules, reduced in number and with low cubical or flattened epithelium. The convoluted tubules are also small, lined by the same type of atrophic epithelium and reduced in number. Many glomeruli are merely fibrous knots, others are in various stages of atrophy, a few surviving more or less unaffected. There is an increase of interstitial tissue, due partly to the collapse and atrophy of the essential elements of the kidney, partly to actual proliferation. Groups of lymphocyte-like cells are often seen dispersed amongst the interstitial tissue. The blood-vessels are usually sclerosed.

The disease may be **unilateral** or **bilateral,** and in the latter case the cause is usually to be found in some form of obstruction to the urethral outflow.

Causes of Unilateral Hydronephrosis. These are blockage by a calculus which may lodge at the commencement of the ureter, or in its lumen, usually as it passes through the vesical wall : narrowing of the ureter from inflammatory changes either in it or in neighbouring parts, *e.g.*, where a ureter has become involved in the fibrosis around a psoas-abscess. An abnormal renal artery entering the lower pole of the kidney may cause kinking of the ureter over it (Fig. 523). Congenital narrowing of the exit of the ureter from its pelvis, or undue elongation of the ureter may cause S-shaped bends and kinking (Fig. 496, p. 853) ; compression of the ureter by tumour or from lymph-nodes invaded by tumour, or injury to it during surgical procedures or child-birth, may lead to its obstruction.

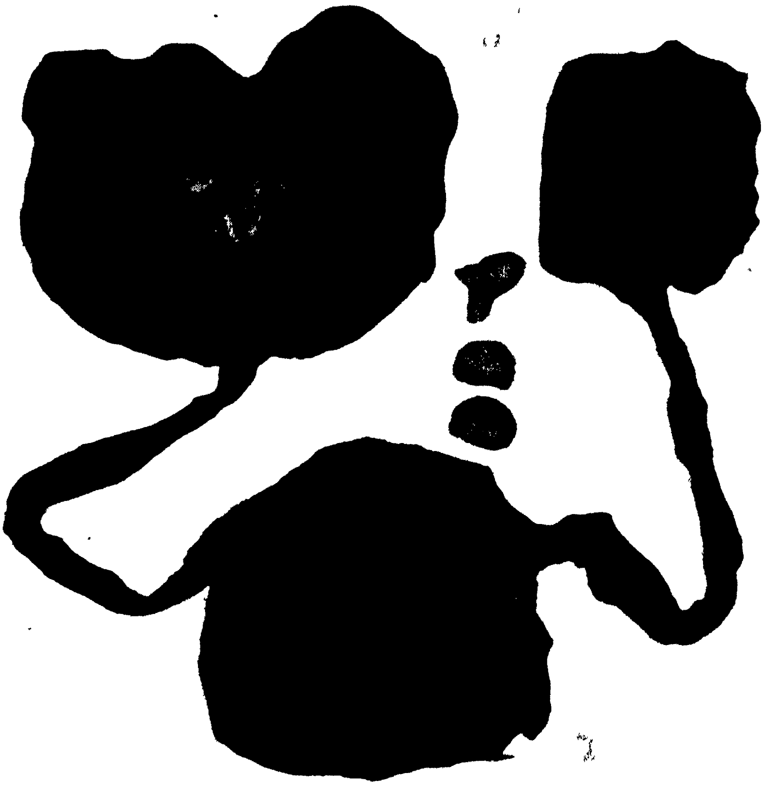


FIG. 524. *Bilateral Hydronephrosis due to Bilateral Renal Calculi.* Both kidneys show advanced hydronephrosis, that on the right side of the illustration being more so than that on the left. Both ureters are dilated and thickened. Calculi (not now *in situ*) were present in both kidneys and both ureters. Several are shown laid out between the kidneys ; and an opening in the ureter on the right, near the bladder, indicates where a calculus had lodged. In a corresponding position in the other ureter also a calculus was impacted. (Specimen—from a female patient aged 19 years—presented by J. R. Cameron, Esq., F.R.C.S.E.)

Causes of Bilateral Hydronephrosis. In rare instances, bilateral calculi are found obstructing both ureters (Fig. 524). In pregnancy it is common to find a mild degree of ureteral dilatation above the brim of the pelvis, but hydronephrosis, if present at all, is usually slight.

Commonly, the cause is to be sought for in the urethra, especially the male urethra, where stricture or enlarged prostate is frequently responsible. Phimosis is a not infrequent cause in male infants. Congenital atresia of the urethra, a rare abnormality, causes a hydronephrosis present at birth. In the female, chronic inflammatory changes in the broad ligament may constrict the ureters without involving the bladder in the obstructive process. In a case examined by us some years ago (Fig. 525), this had occurred and had led to almost complete obstruction of three ureters, two on one side and one on the other. The inflammatory condition pre-dated death by three years, by which time a pronounced degree of hydronephrosis with extreme renal atrophy was present. Death resulted from a mild infection of the scanty shell of surviving kidney-tissue.

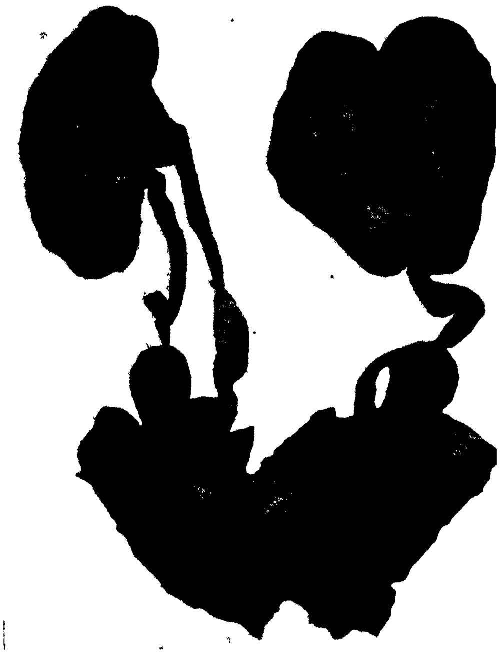


FIG. 525. *Bilateral Hydronephrosis from Chronic Parametritis in the Broad Ligament.* The kidney to the left of the figure had two ureters, both are dilated and thickened. These, together with the single ureter of the other kidney, were constricted by dense fibrosis at the base of the broad ligament; the uterus and bladder have been divided and turned aside to show this. From a woman aged 36 years.

Tumour of the bladder is occasionally responsible for ureteral obstruction. Injury to the lower lumbar and sacral cord or nerve-roots, or pressure on them by tumour may cause a paralysis of the bladder and its inability to empty itself. It becomes distended, and this reacts on the ureters, causing hydronephrosis. Usually, the condition is complicated by cystitis and ascending infections.

In the bilateral form, both kidneys show the type of change already indicated, but often in differing degree. If the obstruction is slowly produced, there may be extreme atrophy of both kidneys before they finally fail. Often some patches of kidney-tissue survive and so sufficient function to maintain life is still possible. The ureters are dilated and, depending on the cause and superadded changes, they may be greatly thickened. If the obstruction is in the urethra, the bladder is involved. It is dilated and, in time, becomes hypertrophied. Herniation of its mucosa may take place between the muscular trabeculæ of its wall and diverticula be produced.

Results. In the case of unilateral hydronephrosis, the result may be merely the atrophy of the kidney which shrinks and contracts, or remains as a thin-walled sac of fluid. The other kidney is able to maintain function. Where the condition is bilateral, the results are more serious. Owing to the gradual atrophy of renal tissue, renal inefficiency supervenes, with death from uræmia. Usually, the issue is precipitated by superadded infection.

FIG. 526. *Renal Carcinoma* (sometimes misnamed a " Hypernephroma "). The tumour occupies the upper pole of the kidney, and has invaded the renal pelvis and renal vein. Extensive hæmorrhage (dark areas) has occurred into the tumour-tissue.

Such infection is always liable to occur in hydronephrosis, particularly where the bladder also is involved, as in the case of stricture of the urethra or enlarged prostate. Infection of the bladder leads to cystitis ranging from a mild catarrhal process to severe purulent inflammation with ulceration of the mucosa. Infection extends up the dilated ureters, probably *viâ* the lumen itself, to the stagnant pools in the pelves, and a pyelitis and pyelonephritis result, with renal failure and death (pp. 864–5). Patients may survive such a pyelonephritis, but later examination shows a kidney, or kidneys, grossly scarred and atrophied, with thickening of the pelvis. It is one form of granular contracted kidney, or chronic nephritis, of inflammatory origin from the lower urinary tract, and not, as in the previously-described examples of nephritis, from the blood-stream.

The fluid in a hydronephrotic kidney is, at first, of the nature of urine, but later, its composition alters as inflammatory changes supervene, in which case it may become purulent—a pyonephrosis (pp. 865 and 890).

TUMOURS OF THE KIDNEY

SIMPLE TUMOURS:—

The commonest is the **fibroma** (*see also* p. 301) in the form of a small, pearly white, firm, spherical nodule, some 2 to 5 mm. in diameter, usually situated in the pyramid, and occasionally multiple. They are of little practical importance. A simple **adenoma** is not infrequent. This tumour is small, some 2 to 3 mm., though larger forms, up to 2 or 3 cm. in diameter, may be found more rarely. It is situated near the surface, under the capsule, as a small yellowish nodule. Such nodules were, because of their yellow-ochre colour, formerly regarded as aberrant portions of suprarenal tissue; but, while such may occur, the majority prove to be of adenomatous character, with acini of low columnar epithelium, often containing lipoid particles, and sometimes showing a papillary arrangement. These tumours may possibly be the starting-point of the more malignant forms described below.

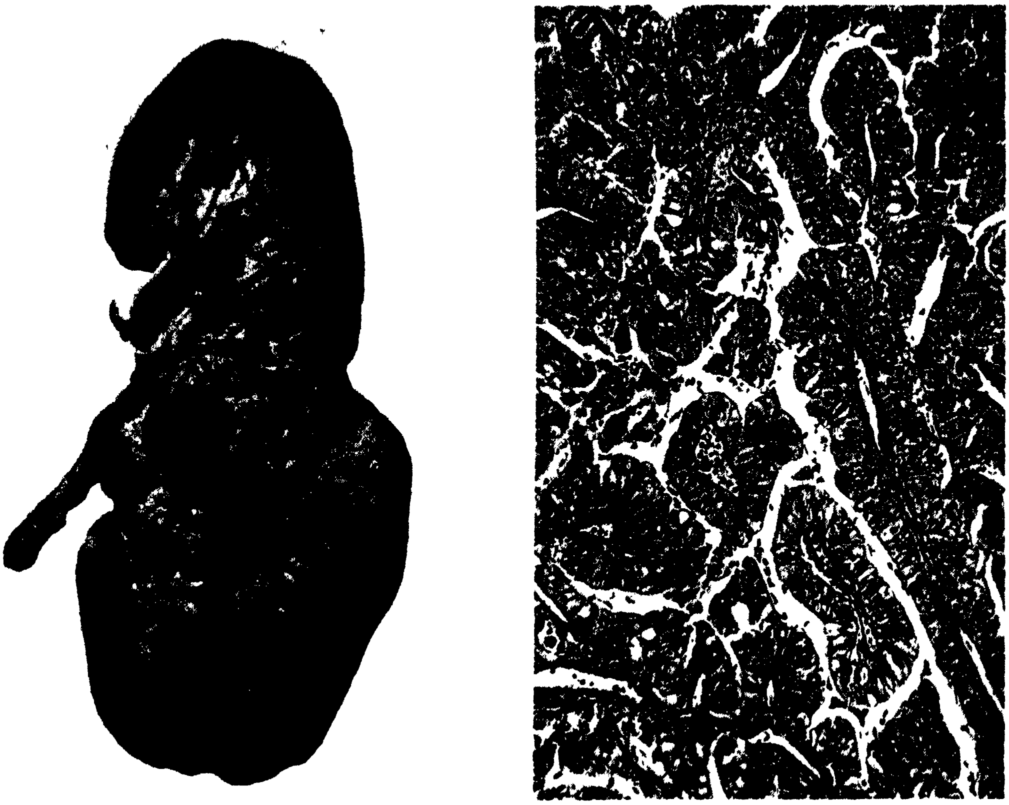
Lipomas may be found occasionally, either in the perinephric fatty tissue or embedded in the cortex.

Angioma—usually of cavernous type, is a rare tumour. It may be in the form of a circumscribed mass or be more diffusely-arranged in the form of a series of dilated thin-walled vessels or " telangiectases." Clinically, hæmaturia is a common sign.

MALIGNANT TUMOURS:—

The common form found in the adult is the " Grawitz-tumour," often misnamed a " **hypernephroma** " (Figs. 526–7), originally so called because by that author it was supposed to originate from a suprarenal " rest " in the kidney. Such tumours are more correctly regarded as of **renal**, *not* suprarenal, origin, *i.e.*, **renal carcinomas,** both on account of their structure and because they do not produce functional effects of excess of suprarenal tissue as do true tumours of the suprarenal itself (p. 847). They have a white or yellowish structure, sometimes with cystic spaces and often showing areas of hæmorrhage or necrosis. They are usually of slow growth, but may ultimately attain a large size, even several times the size of the kidney itself. They grow into and destroy the renal tissue, invade the renal veins and the pelvis of the ureter. Because of this invasive character, the growth may extend into the vena cava and shed metastases to the lungs, from which, in turn, secondary growths in the brain can take place. Hæmaturia is a common clinical sign of these tumours.

The tumour may be of several histological types, and these may all be found in different areas of the same tumour. The commonest variety consists of irregular acini of large cubical or columnar epithelial cells separated by a scanty vascular stroma. Other examples have a papilliform arrangement of long processes of similar epithelial cells arranged on a delicate connective-tissue core containing vessels. The processes are packed together, giving a compact appearance to the tumour. Still others consist of acini of large clear cells. In all forms, hæmorrhage, both old and recent, into the tumour is common, often obscuring much of its structure. Necrosis is also frequent. Different examples vary much in malignancy and rapidity of growth. In those growing more slowly, the kidney-tissue is often clearly demarcated from the tumour and is destroyed by pressure rather than invasion—though veins and renal pelvis may be penetrated.



(A) (B)

FIG. 527. *Renal carcinoma* removed by Sir Alfred Webb-Johnson from a man aged seventy. (A) *Naked-eye photograph of the tumour*, which occupied the lower pole of the left kidney (a glass rod has been inserted into the ureter), and showed a general yellow-ochre colour mixed with paler yellowish areas and necrotic and hæmorrhagic patches. (B) *Low-power view of section of the tumour*, showing its general papilliform structure. In other more compact portions of the mass, the cells had come to simulate those of the suprarenal cortex, and were practically indistinguishable, for example, from the suprarenal adenoma illustrated in Figs. 493–4 on p. 847, this, along with their colour, accounting for the old view that these tumours in the kidney were "hypernephromas." Hæmatoxylin and van Gieson. × 100.

In the infant or child, the commonest renal tumour, and indeed one of the commonest tumours of childhood, is a mixed tumour or **nephroblastoma**, often known as " Wilms' tumour " (Fig 528) ; only rarely does this type occur in the adult. It may attain a very large size, but is less likely to give rise to metastases than the common renal carcinoma (misnamed " hypernephroma "). It arises in any part of the kidney, or even alongside the kidney, and compresses and destroys the organ. It is white and firm, but may show cystic areas and small patches of hæmorrhage. **Microscopically,** diminutive tubules are seen, some with invaginations of stroma suggesting primitive glomeruli. The stroma varies greatly in amount and character ; it may consist mainly of spindle-cells, amongst which are thin-walled blood-vessels, or there may be muscle-cells, either plain or striped ; cartilage and fat also occur. It is thus a mixed, or embryonal, type of growth derived probably from early renal blastema or primordial tissue. In the adult, a similar tumour may be found, consisting mainly of the primitive tubules.

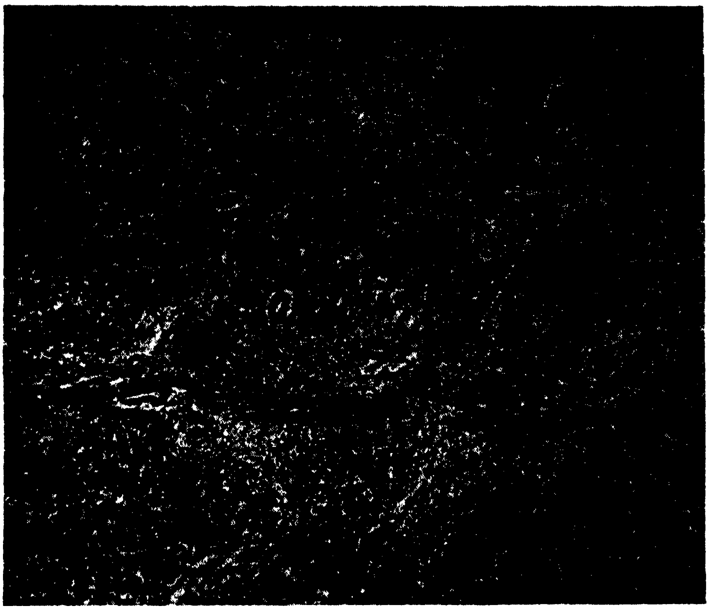


FIG. 528. *Nephroblastoma* or *Renal Blastoma* (" Wilms' tumour ") *from child.* The tumour is composed of a matrix of branching and spindle-shaped cells, scattered amongst which are primitive tubules and glomeruli. Hæmatoxylin and eosin. × 60.

Rhabdomyomas occur as part of the multiple-tumour syndrome of tuberous sclerosis (p. 1134).

True **adrenal** tumours, usually of cortical-tissue type, may be found in the kidney and be recognised by the close resemblance of their structure to that of suprarenal tissue or to that of tumours of the suprarenal itself. Of other tumours, **sarcomas,** round and spindle-celled, are occasionally found arising in the kidney. **Secondary growths** in the kidney are not common, but do occur, especially from bronchial carcinomas and melanotic tumours.

In the pelvis of the ureter, **papillomas** and **papillary carcinomas** arise, and, more rarely, a **squamous epithelioma**. These are sometimes associated with the presence of old-standing calculi in the affected organ.

PARASITES in the KIDNEY:—

Hydatid-Cysts are rare. They may either be confined to the kidney itself or accompany a similar infestation of the liver.

Schistosomiasis (Bilharziasis) may attack the mucous membrane of the renal pelvis.

Eustrongylus Gigas, a very rare parasite in man, has been described as occurring, coiled up within the pelvis of the organ.

SECTION II

DISEASES OF THE URINARY BLADDER

CONGENITAL ABNORMALITIES. Malformations. The main portion of the bladder is formed developmentally from the upper part of the anterior division of the entodermal cloaca; whilst the smaller basal portion, corresponding roughly to the trigone, arises from the expanded lower ends of the Wolffian (mesonephric) ducts, and is, therefore, of mesodermic origin. The upper or cephalic end of the bladder narrows gradually, and is continuous with the proximal part of the allantois, which should normally close about the fifth week of intra-uterine life (Dixon).[1] Owing to incomplete closure of these structures anteriorly, varying degrees of malformation, from **umbilical fistula** up to complete **extroversion of the bladder,** may occur. In the latter anomaly, the anterior wall of the abdomen between the pubes and the umbilicus, and the front wall of the bladder, are deficient. The defective area so produced is lined by the posterior wall of the organ, the margins of which are continuous with the skin of the abdomen. In consequence of the intra-abdominal pressure acting upon the soft, yielding bladder-wall, it is protruded through the incomplete abdominal parietes, forming an irregular, bulging mass, varying in size, and covered by congested, and—from its exposure to bacterial infection—usually inflamed, mucous membrane, on which the openings of the ureters can be seen, intermittently discharging urine during life. With this bladder-condition, there are usually associated malformations of the urethra and external genitals, more especially epispadias or incomplete closure of the urethra along the dorsal aspect of the penis, which itself usually remains small and rudimentary. The pubic arch may be incomplete towards the middle line.

Minor degrees of non-closure are also found, either at the upper, or at the lower, end of the original cleft. The urachus or intra-abdominal portion of the allantoic canal may remain patent, producing a urinary fistula running from the apex of the bladder up to the umbilicus, where it opens on to the surface. In other instances, only certain portions of this canal persist unclosed, and may, by their subsequent distension, give rise to cystic formations. From defective closure at the lower end, varying degrees of epispadias are produced (p. 902).

INJURIES. Rupture of the bladder, with **extravasation of urine** into the peritoneal cavity or into the cellular tissue, may occur, especially in crushing injuries causing fracture of the pelvis, and if the bladder is distended with urine at the time of the accident. Injury to the organ may be produced by penetrating wounds, or during parturition; and also in cases of falls from a height, or blows on the abdomen when the bladder is distended with urine.

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[1] A. Francis Dixon, "Uro-Genital System," in Cunningham's "Textbook of Anatomy," 1937, 7th ed., p. 752, Oxford University Press.

For a detailed account of these and allied conditions, reference should be made to textbooks on Surgery, Midwifery, and Gynæcology.

Dilatation of the bladder, with or without **hypertrophy** of its muscular walls, is of comparatively common occurrence. **Acute distension** may be due to obstruction of the outflow of urine, *e.g.*, from congestion of the prostate, especially where the so-called " middle lobe " of the gland is enlarged. Such acute distension may be due also to paralysis of the muscular coat of the organ, and may be great in degree.

Where the dilatation is **gradually** produced, *e.g.*, in cases of urethral stricture, a considerable degree of hypertrophy may occur, uniform in some cases, but in others asymmetrical, the thick interlacing bundles of muscle, when viewed from within, often coming to resemble the pectinate muscles of the heart. Between these bundles, pouch-like dilatations or **diverticula,** sometimes of considerable size, may be produced—a condition known as **sacculation of the bladder.** When once formed, such diverticula tend to become progressively larger. In these saccules, **calculi** may form, deposits of triple phosphates being common, especially if any infection leading to decomposition of the urine has occurred. Diverticula may also be congenital in origin, *e.g.*, those arising from a persistent urachus (*see above*).

Hæmorrhage into or from the Bladder. Apart from conditions in which the blood reaches the bladder from above, *e.g.*, from the kidney or renal pelvis, hæmorrhage takes place in cases of trauma (accidental or operative), in calculus-formation, in blood-diseases (*e.g.*, hæmophilia, scorbutus, etc.), in some cases of poisoning (*e.g.*, with cantharides), in certain acute forms of cystitis, and in tuberculous ulceration, new growth, and schistosomiasis (Bilharziasis or endemic hæmaturia). Bleeding from the bladder-wall may also be produced if the urine from an over-distended bladder be too quickly drawn off. This is due to the sudden refilling and rupture of vessels which, owing to the pressure upon them of the contained urine, have been rendered temporarily functionless and have undergone degenerative changes. In chronic venous obstruction, *e.g.*, by old inflammatory adhesions, tumour-growth, etc., the veins of the submucous coat of the organ occasionally become varicose, and, from their rupture, give rise to hæmorrhage.

CYSTITIS. Inflammation of the mucous membrane of the bladder varies greatly in its intensity, minor degrees of cystitis being comparatively common. It may occur alone, but is often associated with pyelitis, urethritis, prostatitis, etc.

Causes. Cystitis arises from the irritation of calculi, of new growth, or of the ova of *Schistosoma hæmatobium* (*Bilharzia*) (p. 386) ; but, in most cases, and even in those just mentioned, it is commonly due to bacterial infection, patients suffering from spinal and other lesions causing paralysis of the bladder being particularly liable to infections of the urinary tract (*cf.* p. 864). Bacteria may gain access to the bladder :—

(*a*) **From below, by way of the urethra,** *e.g.*, from the use of a dirty or unsterilised catheter, especially in cases of paraplegia and other affections of the spinal cord ; or the bladder may become infected by the upward extension of a gonorrhœal or other form of urethritis. In the female, ascending infection is specially common after defloration and parturition, and is due most frequently to bacilli of the " colon " type often along with streptococci.

(*b*) **From above, by way of the ureters,** for example in suppurative or other infective diseases of the kidney (p. 862 *et seq.*).

It may here be noted that, in the kidney, bacteria may pass from the blood into the urine without any apparent gross lesion such as ulceration ; and, in this way, bacteria, in some cases, reach the bladder. The presence of bacteria in the urine—**Bacteruria** or **Bacilluria**—does not necessarily, however, give rise to any special inflammatory lesions in the bladder or urinary passages. Bacteruria is very commonly present in typhoid and paratyphoid fevers—the causal organism being passed, often in considerable numbers. Another form of bacteruria, which is comparatively common, is that following a cystitis, pyelitis, or combination of these conditions, in which the inflammatory reaction gradually dies down but the organisms persist, sometimes in large, sometimes in small, numbers. Cases of this nature are liable to relapses or recrudescences of the inflammatory condition when exposed to chill or other predisposing cause—a common sequence of events in, say, *Bacterium coli* bacilluria.

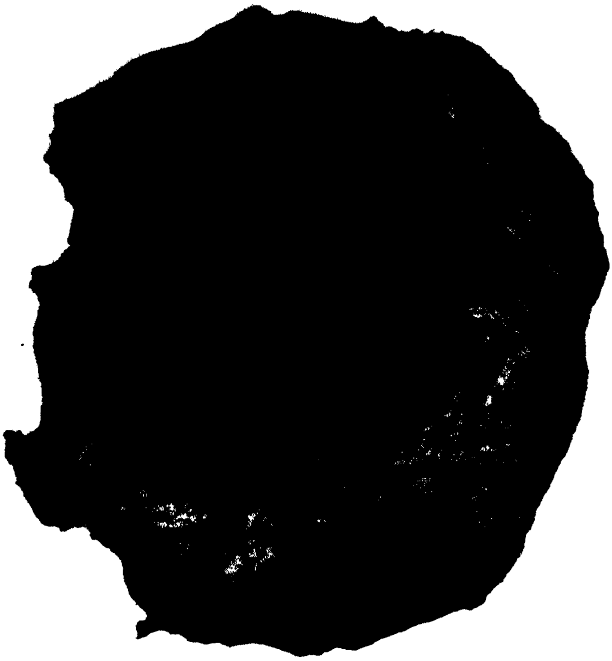

FIG. 529. *Villous Papilloma of Bladder.* The tumour is growing from the region of the trigone and is composed of delicate wavy processes.

(*c*) **By Way of the Blood- or Lymph-Stream.** The bladder may become infected from the intestine, through the weakened or damaged walls of which, organisms, *e.g.*, *Bact. coli*, may pass and find their way by blood- or lymph-stream into the bladder. Such passage of organisms by these channels, however, probably, in the majority of instances, takes place through the kidneys, as described above.

The bacteria most frequently found in cystitis are the *Bact. coli* group, staphylococci and forms of streptococci, and *B. proteus*. In many cases, such infections are **mixed** in character. Certain organisms which lead to alkaline decomposition of the urine may produce cystitis, with a deposit of ammonium urate and phosphates on the mucous membrane. Except where this occurs, the urine, in cases of cystitis, is usually acid when passed, though it rapidly undergoes decomposition and becomes alkaline on standing.

Morbid Appearances. The mucous membrane is congested, swollen, and often thrown into folds. It is sometimes much discoloured, varying from dark-red to purple, and perhaps showing numerous extensive submucous hæmorrhages, the appearance sometimes almost suggesting that of gangrene. The surface may be covered by a red or yellowish-red deposit of precipitated ammonium urate, uric acid, or earthy phosphates, and the summit of the ridges with mucus, muco-pus, or, in some cases, with almost pure pus. The distribution of the inflammatory phenomena may be general, but is often more intense at the base or trigone. The openings of the ureters may show localised congestion, œdematous swelling and hæmorrhage, particularly when there is associated pyelitis.

When the inflammatory condition has become chronic, the bladder-wall is often greatly thickened, this being due mainly to an overgrowth of fibrous tissue in the wall, though some degree of hypertrophy of the muscular coat can occur. Varying degrees of contraction are liable to supervene, and, in some instances, the cavity is reduced to a minimum.

TUBERCULOSIS of the BLADDER. *See under* **Genito-Urinary Tuberculosis,** p. 72.

NEOPLASMS of the BLADDER. These are most frequently **papillomatous** in type—either simple, or, perhaps more commonly, malignant in nature, the one group running into the other without any definite line of demarcation between them. They are characterised by the presence of masses of long, delicate branching villous processes, which consist usually of a scanty, highly vascular connective-tissue core, covered by transitional stratified epithelium, resembling that of the normal bladder, though the more flattened superficial cells are often absent (Fig. 163, p. 330 : and Fig. 529 opposite). In simple papillomatous tumours, the condition is limited to the mucous coat, but, in those which are malignant, widespread infiltration takes place. All intermediate grades are found. Hæmorrhages from such tumours are frequent, and small portions of the tumour tend to become broken off and are found on microscopical examination of the urine.

Scirrhous tumours, though occasionally primary, are more usually secondary, especially to tumours of the prostate ; and the same holds good with regard to those of adenocarcinomatous type. Fibroma, myxoma, myoma, and sarcoma are rare. Cysts are very uncommon, but may originate from glands or from congenital defects connected with the urethra, urachus, Wolffian body, or Gärtner's duct (epoöphoron) (pp. 353–4).

Malakoplakia[1] is a rare condition which attacks the mucous membrane of the bladder. It is characterised by the presence of slightly raised pale-whitish or yellowish-white opaque areas scattered over the surface, due to the development, mostly in the submucous coat, of masses of large polygonal cells, many of which contain clear rounded "Michælis-Gutmann bodies," staining deeply with hæmatoxylin, and believed by some writers to be degeneration-products, whilst others think that they may be organismal. The nature of the condition is still unknown, various authors having suggested that it may be neoplastic, granulomatous, or bacterial in origin, others that there may be more than one factor in its causation. This disease may also attack the kidney.

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[1] "Malacoplakia (Malakoplakia) Vesicæ : an Investigation of Certain Mycotic Infections of the Genito-Urinary Tract," by Carnegie Dickson, Charles Gray and Frank Kidd, *Urologic and Cutaneous Review*, St. Louis, Mo., U.S.A., 1927, **31,** 611–621 (*note* : no proofs of this article were seen by the authors before its publication—hence the many misspellings and errata in it) : and "Malakoplakia of the Urinary Bladder," by A. E. Chisholm and G. R. Tudhope, *Edin. Med. Jour.*, 1934, **41,** 626–9. In subsequent papers by other writers, micro-organisms of this group have been referred to as "*Bacillus moniliformis*."

PARASITES in the BLADDER. The only parasite of importance which affects the urinary bladder is *Schistosoma hæmatobium* (*Bilharzia hæmatobia*), a description of which will be found on p. 386. Carnegie Dickson (with Thomson Walker and others) has investigated about a dozen cases of urinary infection with **mites** (p. 430).

DISEASES OF THE URETHRA

MALFORMATIONS. **Absence** of the urethra, in whole or in part, **doubling** of the channel, abnormal communications (*e.g.*, with the rectum), **diverticula,** and other rare abnormalities, may occur. The commonest and most important malformations are **hypospadias** and **epispadias.**

Hypospadias is the result of varying degrees of non-closure of the floor of the urethra. The anterior orifice of the complete portion of the channel may open on the surface at any point from the glans in front to the perineum posteriorly. In its most extreme form—the condition known as **pseudo-hermaphroditism**—the urethral opening is in the perineum; the scrotal integuments show a central vertical cleft simulating the aperture of the vulva; and the penis is rudimentary and resembles a hypertrophied clitoris. The testicles may not have descended, or may be misplaced. In its lesser degrees, the anterior opening of the urethra is in front of the scrotum on the under aspect of the penis. In its commonest form, the deformity is slight, the aperture being on the under aspect of the glans in the position of the frænum, which is imperfect or absent. The artificial production of hypospadias is practised by some native races in Africa and elsewhere.

Epispadias is a condition in which the urethral wall is defective upon the dorsal aspect of the penis. The opening may be on the upper aspect of the glans. More commonly, however, it is at the root of the penis under the symphysis pubis. In its most complete form, it constitutes part of the condition of extroversion of the bladder (p. 898).

INJURIES of the URETHRA occur from lacerated wounds of, or occasionally from falls upon, the perineum—the passage in the latter instance being "nipped" against the lower edge of the pubic arch. **Tearing of the urethra**—especially at or near the triangular ligament—is a common complication of fracture of the pelvic bones; whilst false passages can be produced by the unskilful use of the catheter in cases of stricture, or by the introduction of foreign bodies. These injuries are of importance from the fact that they give rise to extravasation of urine into the surrounding tissues, and also because any such injury may lead later to cicatricial contraction and the production of urethral stricture, or to its exaggeration if already present.

INFLAMMATORY LESIONS. The most important of these is the inflammation produced as a result of gonorrhœa (p. 905). In the acute stage, the mucous membrane is red and swollen and there is a glairy discharge which soon becomes purulent and usually slightly blood-stained. It contains numerous polymorphonuclear leucocytes and also mononuclears and desquamated epithelial cells, in the interior of which—especially in the polymorphs—the causal organisms, often in large numbers, are found. The gonococci (*Neisseria gonorrhœæ*) penetrate deeply into the mucous membrane and the subjacent connective tissue, where they can persist for a long period. They may also infect the prostate, seminal vesicles, testicles and bladder ; and, in the female, may produce gonorrhœal cervicitis, endometritis, salpingitis, and peritonitis. One of the most important complications is arthritis or "gonorrhœal rheumatism" (p. 1234). Secondary mixed infection with other organisms frequently occurs comparatively early. Gonorrhœal urethritis, unless adequately treated, usually persists as a chronic inflammation for a considerable period after infection, and is the commonest cause of stricture.

Other forms of urethritis are comparatively rare.

STRICTURE of the URETHRA may arise from cicatricial contraction following injury or inflammation. It is most commonly gonorrhœal in origin. The most frequent site of such strictures is at or immediately in front of the triangular ligament, *i.e.*, at or near the junction of the membranous with the spongy portions of the canal. From the resulting retention of urine, the urethra above the stricture, the bladder, and perhaps also the ureters and renal pelves, become dilated, and considerable hypertrophy of the bladder frequently ensues.

Urethral Calculi. These may be due to impaction from above, or are in some cases primary. In the latter instance, they are usually phosphatic in nature, may be multiple, and sometimes attain to a considerable size.

Tumours of the urethra are rare. Papilloma, fibroma, myoma, adenoma, carcinoma, sarcoma and cysts have been described.

Urethral Caruncle in the female is a projecting, bright-red vascular overgrowth of the mucous membrane, chronic inflammatory and *not* neoplastic in nature. It develops, mostly in elderly women, on the posterior wall of the urethra near or in the meatus. It is covered by squamous epithelium.

CHAPTER XXVI

DISEASES OF THE REPRODUCTIVE SYSTEM

SECTION I

MALE REPRODUCTIVE ORGANS

In addition to the primary function of spermatogenesis, an important internal secretion, the male **sex-hormone,** is produced in the testis by the interstitial cells of Leydig lying between the gland-tubules. The growth and development of the seminal vesicles and prostate are influenced by this sex-hormone, which, however, has no effect on the seminiferous tubules. Thus, if the testes are removed before puberty, further development of the prostate and seminal vesicles is prevented, and the special secondary sexual characteristics, such as development of hair on the face or trunk do not appear and the normal enlargement of the larynx at puberty does not take place, the epiphyses of the long bones may remain longer unossified, and the bones tend to be thinner and more elongated than normal. Castration after puberty produces comparatively slight changes, though the prostate tends to atrophy, and the secondary sexual characters may become less marked. Changes in metabolism are observed and there is a tendency to adiposity.

The anterior lobe of the pituitary, by means of its gonadotropic hormones, directly controls spermatogenesis, the secretion of the testicular sex-hormone and probably also the descent of the testicle. In immature male animals, anterior-lobe transplants from fully developed adults bring about premature development of the accessory organs of reproduction, especially the seminal vesicles, and may cause precocious secretion of seminal fluid. On the other hand, in any condition of the pituitary in which there is hyposecretion, testicular atrophy will follow, with diminution of testicular sex-hormone and atrophy of the seminal vesicles. Experiments on castrated animals suggest that the gonads have an inhibitory action on the gonadotropic hormones of the anterior lobe of the pituitary, for, in such animals, the gonadotropic effects of the pituitary-secretion are said to be more potent than in non-castrated animals. There seems little doubt that other endocrine organs are also related in their activity to the gonads. Castration prolongs the period of persistence of the thymus gland. Congenital absence or maldevelopment of the thyroid (*e.g.*, in cretins) results in non-development of secondary sex-characters; and, in myxœdema, disturbances of sexual functions, such as amenorrhœa in females and impotence in males, are present. In tumours of the adrenal cortex, precocious sex-development occurs in children. Reference has already been made to the influence of the male sex-hormone upon the growth and development of the prostate and to the secretion by the testicle of hormones allied to those produced in the ovary. The injection of œstrone—the principal ovarian hormone—into castrated rats or mice is followed by hyperplasia of the prostate. In non-castrated, healthy rats or mice, the injection produces no characteristic change ; and in the castrated animals, if the male sex-hormone is injected as well as the œstrone, the hyperplasia does not occur. In the enlarged prostate of these animals, the histological changes are similar to those which are associated with the enlarged prostate in old men. These experiments suggest that the disease in the human subject may be due, at all events in part, to an alteration in the relative proportions of œstrone and the male sex-hormone present—the former predominating.

The testicular hormones are members of the **sterol-group** and it has been shown that certain members of this group are potent cancer-producing agents. It has therefore been suggested that, in certain instances, abnormal secretion of these hormones may be responsible for tumour-growth.

For further reference to this subject, *see* Chapters XII on Tumours, p. 291, and XXIV on Diseases of the Endocrine Organs, p. 806.

INFLAMMATION of the male generative tract is due most frequently to **gonorrhœal infection** (*cf.* p. 902), commencing as an acute inflammatory swelling of the subepithelial tissue at the meatus, spreading to a varying extent along the urethra and producing a thick, viscid, purulent discharge, which on **microscopical examination** shows large numbers of polymorphonuclear leucocytes and mononuclear cells in which numerous gonococci (*Neisseria gonorrhœæ*) are found.

This acute stage subsides with, especially under careful treatment, a complete cure ; or the disease may become chronic—and the discharge from the urethra scanty, thin and watery in consistence with usually some purulent "threads." The gonococci may be very few in number, but the condition, **gleet,** remains infective, and the inflammation may spread to the posterior part of the urethra and the prostate. In some cases, an acute prostatitis occurs (p. 915) and a further extension along the vas deferens to the epididymis, or even to the body of the testis. Spread to the bladder is less common, and, in cystitis following an attack of gonorrhœa, the gonococci are usually associated with other pyogenic organisms.

At a later stage, localised overgrowth of fibrous tissue may produce stricture of the urethra, which in turn leads to dilatation and hypertrophy of the bladder. The bladder frequently becomes infected by other pyogenic organisms and the septic cystitis so produced may be followed by pyelitis and suppurative nephritis. Overgrowth of fibrous tissue may occur also in the testes, leading to obliteration of the tubules and the production of sterility.

In cases of acute gonorrhœa, the organisms may be carried by the blood-stream to distant parts and give rise to inflammatory lesions in the joints, sheaths of tendons, pleura, pericardium, and, more rarely, endocardium, and meninges. Though gonococci are the commonest bacteria found in inflammatory lesions of the urethra, it must be recognised that other pyogenic organisms may sometimes be causal, and, in some cases, the urethritis is secondary to cystitis.

THE TESTICLE

MALPOSITIONS. The testes are developed within the abdomen, from which they should normally descend into the scrotum during fœtal life. **Cryptorchidism** or **Undescended Testicle** is the term applied to the condition where the descent has, either totally or partially, failed to occur. It may affect one or both organs, and the arrest may take place at any part of their downward course. Thus, the testis may be retained within the abdomen, or in the inguinal canal. The undescended organ is, as a rule, imperfectly developed and functionless as regards spermatogenesis, though the specific internal secretion is still usually produced by the interstitial cells, which are generally unaffected. The condition is of importance from the increased liability of the gland to injury, or to become the seat of inflammation or neoplastic growth (*see* p. 909 and Figs. 533 to 536). In some cases, apparently from abnormalities in the attachments of the gubernaculum testis, the organ may find its way into the perineum or elsewhere. Reference has been made above to the influence of certain elements of the secretion of the anterior part of the pituitary gland upon the descent of the testicle, and Spence and Scowen (1935) claim that, in cases of undescended testicle, the organ has, as the result of treatment with gonadotropic hormone, entered the scrotum and that its functional capacity has been improved. In this connection, however, it must be kept in mind that not infrequently the descent of the testis is completed naturally at or just before puberty.

In some parts of India, during the training of boys to become professional athletes, particularly wrestlers, the testes are, for safety, habitually pushed up out of th scrotum ; and instances of the rejection by members of the Indian Medical Service not acquainted with this practice, of such athletes as recruits, on the grounds of " undescended testicle," are not unknown.

MALFORMATIONS and other congenital abnormalities occur : for example, the non-development of one or both organs, or, in rare instances, the occurrence of a third testicle.

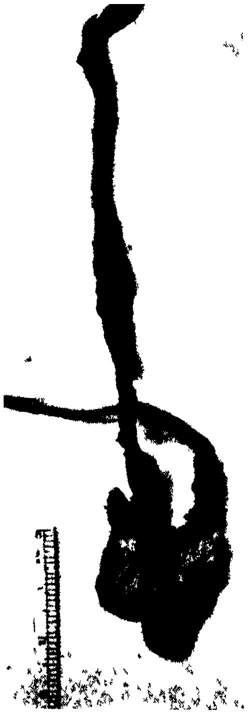
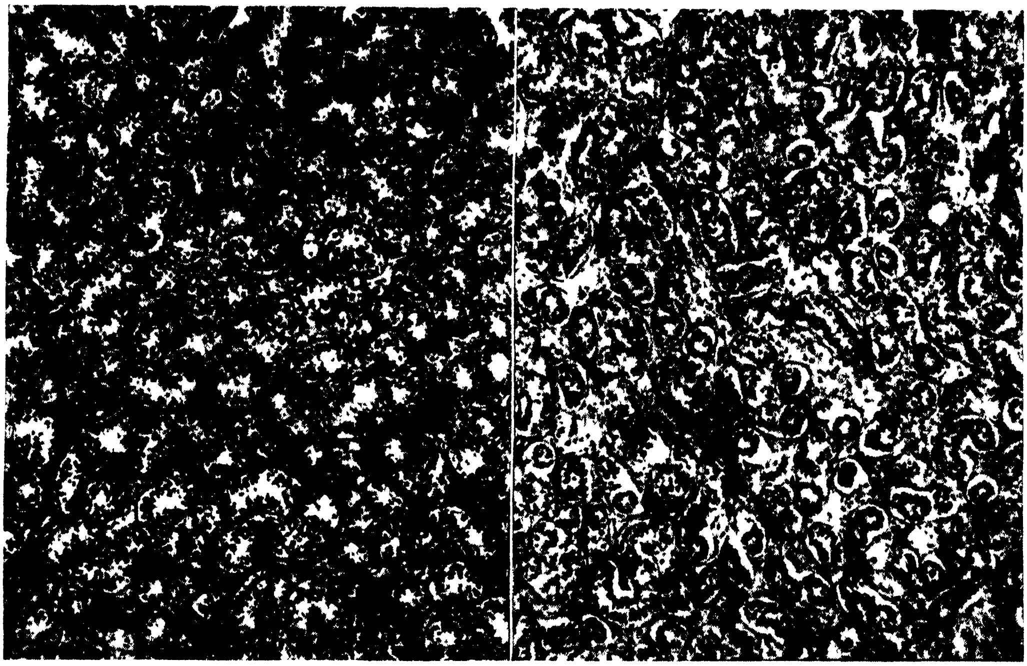


FIG. 530. *Undescended left testicle* in a man of forty-one years. The organ was situated in the inguinal canal and consisted mainly of epididymis from which the vas deferens is seen curving to the left in the photograph. The smaller mass on the left represents the body of the testis. The patient died of metastases from a malignant teratomatous tumour of the right testis, also undescended (*see* Figs. 533–4). × $\frac{2}{3}$ natural size (approx.).

HYDROCELE, or distension of the tunica vaginalis with fluid, which is usually clear and serous, may be dropsical, traumatic, or, more commonly, chronic inflammatory in origin. When of old standing, the tunica vaginalis may become much thickened. On the surface of the testicle this fibrous thickening may be irregular and nodular, and is liable to be mistaken, on naked-eye examination, for cartilage. In congenital hydrocele, the cavity of the tunica vaginalis remains in communication with the general peritoneal cavity. If hæmorrhage occurs into the tunica vaginalis, the condition is known as **Hæmatocele.**

ORCHITIS, or INFLAMMATION of the TESTIS, is produced by local infection by way of the urethra and vas deferens, as in **gonorrhœal orchitis:** or from a cystitis due to *Bacterium coli* or other organisms ; or it may be due to a blood-spread, as in **acute infective parotitis or mumps,** in which this complication is of not infrequent occurrence (p. 117).

An orchitis commences usually in the epididymis, where it may remain localised, or from which it may spread to the body of the testicle. Acute hyperæmia and swelling occur, with or without extension of the inflammation to the tunica vaginalis. Recovery may take place, or the disease may go on to abscess-formation, or it may become chronic. In mumps, the lesion usually is a diffuse inflammatory swelling of the testicle, and is never suppurative, but chronic changes with fibrosis and atrophy may follow.



Right testis : Scrotal. *Left testis :* In inguinal canal.

FIG. 531. Low-power views for comparison of structure of *a fully descended* and *an undescended testicle* in a boy aged eight years who died of a suprasellar adamantinoma. In the undescended left organ, the tubules are smaller and more widely separated, and contain distinctly fewer epithelial cells. The basement-membrane is more delicate, the connective tissue looser, but containing fair numbers of interstitial cells. Hæmatoxylin and van Gieson. × 100. (W.E.H. case.)

Chronic orchitis is characterised by fibrous overgrowth, with consequent atrophy of the glandular elements. It may, as just stated, originate in an acute attack, or it may be due to one of the chronic infective diseases such as tuberculosis, syphilis, or leprosy.

TUBERCULOSIS of the TESTICLE. The disease commences usually in the epididymis, and is due probably to a blood-infection. The usual phenomena of the disease are seen, viz., caseation and fibrous overgrowth. These may, at first, be localised to the epididymis, which becomes more easily palpable as an elongated firm mass, lying along the posterior border of the testis. The disease tends to extend to the tunica vaginalis and to the body of the gland, which, from the spread and coalescing of the caseous foci, may become entirely destroyed. Ulceration is liable to occur, with the formation of fistulous openings through the skin of the scrotum. Reference has already been made to the tendency of the tuberculous process to spread, by way of the vas deferens, vesiculæ seminales and prostate, to the bladder and kidneys (*see* **Genito-Urinary Tuberculosis,** p. 72).

SYPHILIS of the TESTICLE may take the form of a diffuse chronic inflammatory overgrowth of the connective-tissue framework of the organ : or, of localised **gummatous** formation starting in the body of the testis. In the latter case, the gummata may be multiple, and these necrotic areas may, by their coalescence, cause practically total destruction of the gland (p. 88).

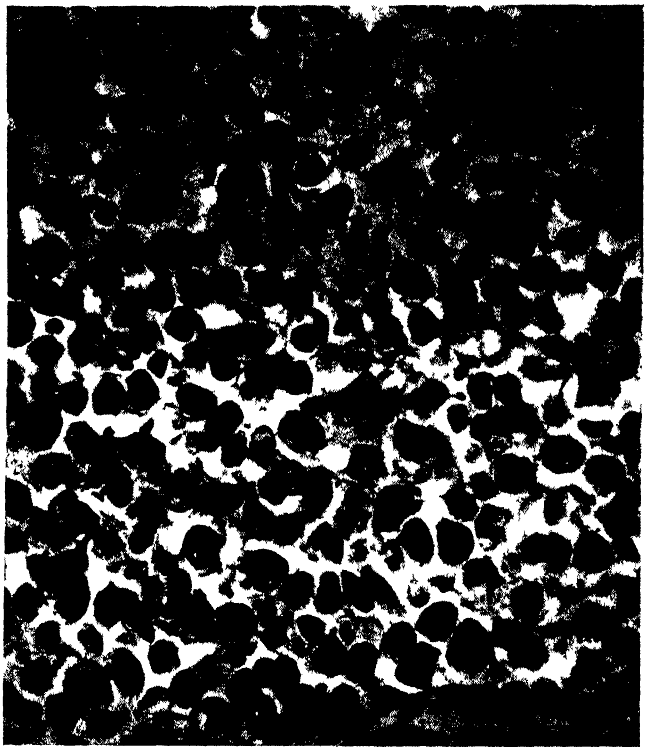


FIG. 532 *Seminoma of the testis*, showing masses of round cells—some with mitotic figures—and very little stroma × 300.

TUMOURS of the TESTICLES. Simple tumours are uncommon, the testicles being much more frequently the seat of malignant disease.

Carcinomas—especially those of the soft or encephaloid type—and **sarcomas,** may occur, the latter often exhibiting a mixed character, for example, combinations with myxomatous, chondromatous, adenomatous, and other varieties of tumour. Mixed cartilaginous tumours of the testicle are of special interest. They are sometimes highly malignant, and have been considered by some writers to arise from remnants or " rests " of aberrant and included vertebral cartilages—the testicle, before its descent, lying in close proximity to the bodies of lumbar vertebræ. They are now, however, believed by most authorities to be **teratomatous** in origin (p. 351), and in support of this view is the fact that, in addition to cartilage, an admixture of other tissues derived from all three embryonic layers is usually present in such tumours (*see* Figs. 535, 536). Not all teratomas of the testicle are malignant, but all appear to have malignant potentiality. It can sometimes be observed that a sarcoma or carcinoma is developing in the midst of trigeminal structural elements, many of which have a fairly orderly habit of growth. It may be that even the seminoma (see below) is thus derived and is to be considered an imperfectly differentiated carcinoma arising in a teratoma.

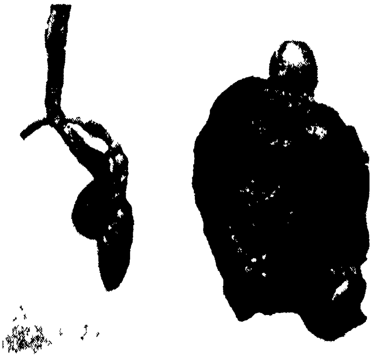


FIG. 533. *Malignant teratoma of right undescended testicle.* Naked-eye photograph of the primary malignant tumour of the undescended right testicle, in a man aged forty-one years, removed by operation (at the Royal Northern Hospital) on March 15th, 1938. The tumour is spongy and hæmorrhagic, with a cystic swelling, probably corresponding to the "hydatid of Morgagni," at its upper end. (For comparison with this is shown the small undeveloped and also undescended left testicle, removed *post mortem* from the inguinal canal of that side (April 11th, 1938), and consisting mostly of epididymis. (Primary-tumour specimen by courtesy of Dr. P. O. Ellison.) × $\frac{1}{2}$ (approximately).

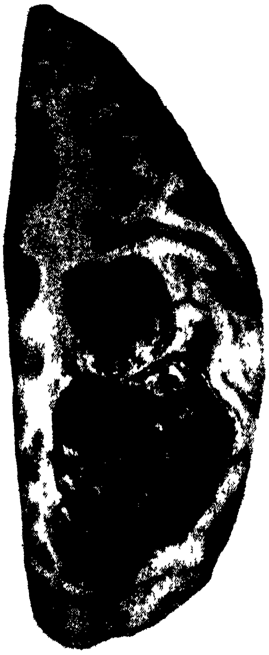


FIG. 534. *Cerebral metastases from malignant teratoma of the right undescended testicle* in a man aged forty-one years (*see also* Figs. 533 and 535–6 from the same patient). Undersurface of a horizontal slice through the left cerebral hemisphere, in which there was an extensive mass of coalescing metastases, of spongy consistency, and containing numerous cystic cavities, one of them of large size, with smooth walls. (W.E.H. case.) × $\frac{4}{5}$ natural size.

Seminomas. Tumours composed of masses of spheroidal or polyhedral cells of varying size, arranged sometimes in alveolar fashion and with comparatively little stroma, are the commonest malignant growth in the testicle. The highly cellular character, the comparative absence of stroma and great vascularity, as well as the frequent occurrence of irregular areas of necrosis and hæmorrhage, led to these tumours being formerly classed as "sarcomas." More recent work, however, has shown that they arise from spermatoblasts, and hence they are now termed **seminomas.** Meyer's view that they arise from the primitive gonad before sex-characteristics are differentiated is supported by the occurrence of similar, if not identical, tumours in the ovary. Metastases frequently occur.

Chorionepithelioma is another tumour of a teratomatous nature which may occur occasionally in the testicle. In the male, it is presumably a " tumour of consanguinity," *i.e.*, derived from a germ-cell segregated very early in development and with potentialities in some ways resembling those of the impregnated ovum itself. Nearly every variety of fœtal tissue may be included in such tumours. In the male, they are always of much greater malignancy than in the female, as, in the case of the latter, the tumour arises from the offspring, and the chorionic tissue may attain a varying degree of maturity, the resulting tumour showing a corresponding variation in its malignancy—a lesser degree being found, the more mature the development of the tissue from which it originates. It is interesting to note that, in many of these cases, for example that illustrated in Figs. 535 and 536, the urine has given the Aschheim-Zondek (" A.Z.R.") and other reactions of pregnancy, in a more marked degree than it is given in the case of other testicular tumours.

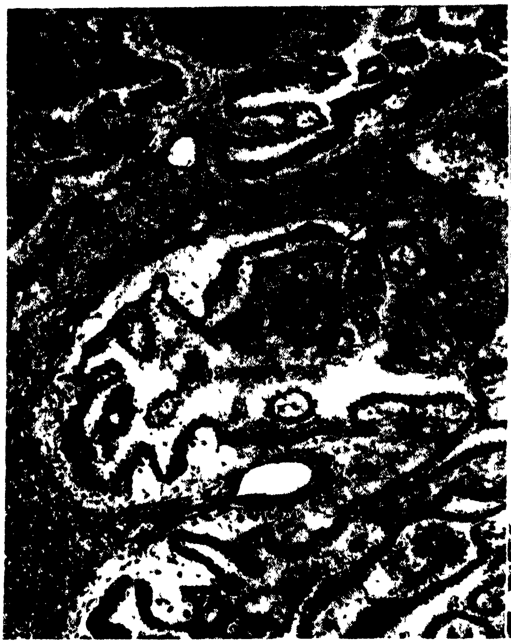


FIG. 535. *Primary malignant teratomatous tumour of undescended right testicle* (Fig. 533). Note the resemblance at parts to chorionic structure. (By courtesy of Dr. P. O. Ellison.) The urine of this patient gave a strong A.Z.R. (*see* below). Hæmatoxylin and eosin. × 100.

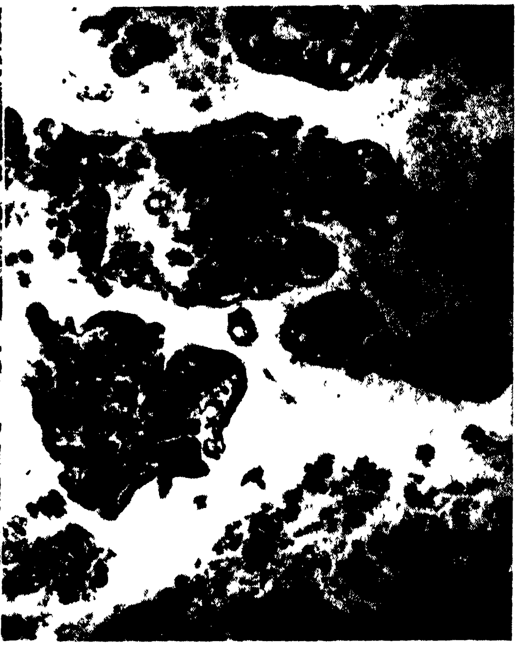


FIG. 536. *Malignant teratomatous tumour of testicle : Metastasis in liver* from the tumour illustrated in Figs. 533-5. Note its close resemblance to chorionepithelioma—both characteristic types of cell being present—the surface syncytial or plasmodial layer, and the subjacent smaller polyhedral cells corresponding to cells of the Langhans-layer of the placental villus. Hæmatoxylin and eosin. × 100.

Cystic tumours of the testicle sometimes occur, in which the organ is transformed into a congeries of dilated cysts, originating possibly from the developmental intermingling with the remains of the Wolffian body or neighbouring structures (pp. 353–4).

THE SPERMATIC CORD

The commonest disease of the spermatic cord is the condition of **varicocele** or **varicose dilatation of the spermatic veins.** This occurs most commonly on the left side. (*See* under **Diseases of Veins,** p. 500.)

Hydrocele of the cord is due to distension of unobliterated remnants of the peritoneal diverticulum formed for the descent of the testicle, and from the lower part of which the tunica vaginalis testis originates. Hæmorrhage into these remnants, or into the tissues of the spermatic cord, constitutes the condition known as **Hæmatocele** or **Hæmatoma** of the cord.

TUBERCULOSIS of the **vas deferens** occurs as part of the more widespread condition known as **Genito-Urinary Tuberculosis** (p. 72 *et seq.*).

THE PENIS AND SCROTUM

BALANITIS, or inflammation of the integument covering the glans and lining the prepuce, may occur as an independent infection ; or it may be associated with the presence of hard chancre, soft sores or gonorrhœa. Inflammatory affections of these parts are also found in some cases of gout and diabetes.

For descriptions of such conditions as **phimosis** (narrowing of the anterior orifice of the prepuce), **paraphimosis,** etc., reference should be made to text-books of Surgery.

ULCERS, or **CHANCRES,** are of frequent occurrence, especially in the venereal diseases. **Hard chancre** (p. 81) is the primary lesion of syphilis, and is situated usually on the glans, either on the corona or in the neighbourhood of the frænum, and *Treponema pallida* may be found in a scraping from the base and edges of the ulcer, as well as in the juice of the enlarged inguinal lymph-nodes obtained by puncture with a syringe. **Soft sores** or **chancroids** (p. 676) have a similar distribution. They have usually been regarded as due to local infection with Ducrey's bacillus, which may also be found in the buboes or enlarged lymph-nodes in the groin ; but the specificity of this organism has not been clearly established. Soft sores—unlike the hard chancre—are not infrequently multiple. **Condylomata,** flat or papilliform outgrowths of the surface epithelium, are venereal in origin. The flat type (**condyloma latum**) is syphilitic ; but the branching papillomatous form (**condyloma acuminatum**) is found particularly when there has been a chronic gonorrhœal discharge.

TUMOURS. The most important tumour of the penis is the **squamous epithelioma** (Fig. 167, p. 335), which originates usually in or near the glans, forming irregular, warty, fungating masses, which may undergo extensive ulceration. This form of tumour may also attack the scrotum, and, from its comparative frequency among chimney-sweepers, is sometimes called "**Chimney-sweepers' cancer,**" and is, at all events partly, due to the chronic irritation of soot-particles in this region. (*See* pp. 281–2, and *cf.* "**Mule-spinners' cancer**" —*see* footnote on p. 282.)

Elephantiasis of the Scrotum and **Lymph-scrotum** are described on p. 425 *et seq.* (*see also* Fig. 241 on p. 426).

THE PROSTATE GLAND

The prostate gland may be affected by various degenerative, inflammatory, and neoplastic changes, perhaps the most important of these being the enlargement found frequently in elderly subjects. This enlargement, often termed **" hypertrophy " of the prostate,** is, more accurately speaking, a **hyperplasia** affecting the muscular and connective tissue of the organ, with or without glandular proliferation. Where the gland-tissue shows proliferation, there is usually a tendency to the formation of numerous small cystic spaces which may become filled with desquamated epithelium, debris, and the so-called "amyloid bodies." The epithelial cells may be hyperplastic or metaplastic. The causes of this hyperplasia are obscure, but it is probably largely attributable to changes in the activity of the secretion of hormones by the gonads and other ductless glands, with or without the presence of a superadded or in many instances a "residual," chronic inflammatory process—the result, it may be, of a previous gonorrhœa. In many instances, the overgrowth comes to resemble that of a tumour. The enlargement is sometimes uniform, but often it is localised to some particular portion of the gland, especially the central part, which may become enlarged and project into the cavity of the bladder at its neck, constituting the so-called **" middle lobe "** of the prostate. The prostatic portion of the urethra becomes elongated, and perhaps distorted and compressed, giving rise to obstruction to the outflow of urine from the

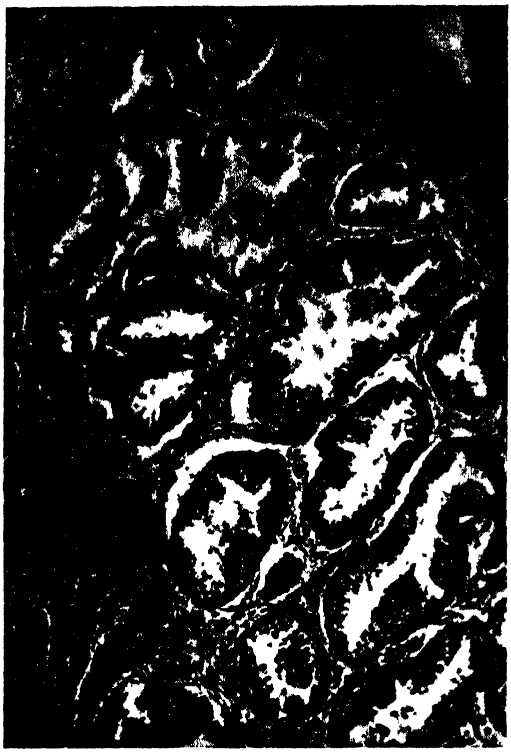


FIG. 537. Section of an enlarged prostate, from an elderly male, showing hyperplasia of the glandular tissue. Hæmatoxylin and eosin. × 75.

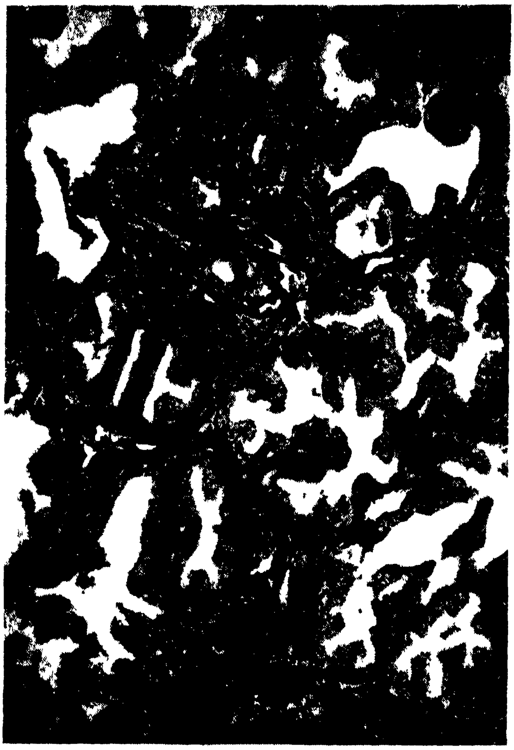


FIG. 538. A similar section from a hyperplastic prostate in which carcinoma developed in another part of the gland (Fig 539). × 75.

bladder. This obstruction, from superadded congestion, may become "acute" or complete. Prostatic enlargement may thus lead to **changes in the bladder** resembling those produced by stricture of some other part of the urethra, viz., **dilatation, hypertrophy** and **sacculation** (pp. 899 and 903).

The "normal" prostate, especially as age advances, varies greatly in its histology in different specimens and in different parts of the same specimen, and this is still more the case in pathological conditions. In adjoining microscopical fields there may be all combinations of catarrhal and other inflammatory phenomena, hyperplasia and simple and perhaps malignant neoplastic growth. In this connection it is important to note that, although hyperplastic and malignant enlargements of the gland are commonest in elderly, they may occasionally be found in younger, patients, for example, the case illustrated in Figs. 538 to 542 was only thirty years of age.[1]

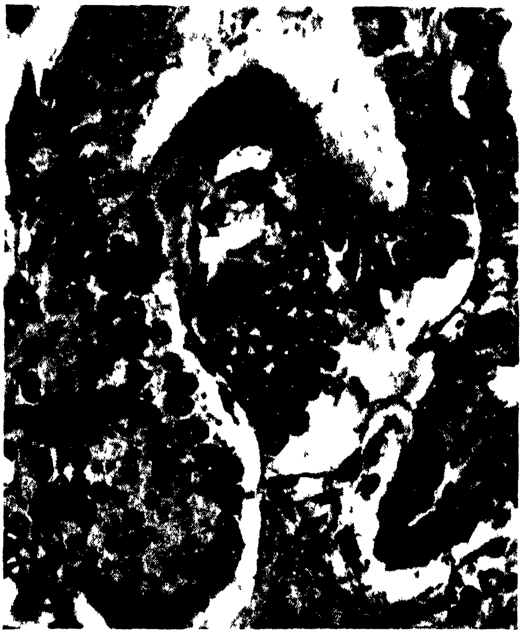


FIG. 539. *Malignant adenoma of prostate* from another part of the same gland as Fig. 538. *See also* Figs. 540 to 542. Hæmatoxylin and eosin. × 400.

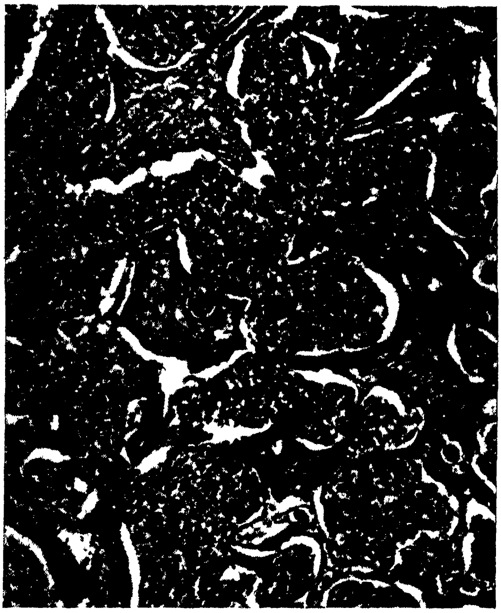


FIG. 540. *Metastasis in a bronchial lymph-node from malignant adenoma of prostate.* From the same case as Figs. 538–9 and 541–2. Hæmatoxylin and eosin. × 100.

Wade[2] classifies the causes of Prostatic Dysuria or "Prostatism" as follows:—

Three outstanding varieties of disease lead to prostatism:—

(*a*) **Prostatic Hypertrophy or Chronic Lobular Prostatitis,** the commonest lesion, present in 82 per cent. of his 134 cases. He considers the condition a senile hyperplasia, an aberrant growth of tissue that is not the result of the occurrence of an independent new growth, but is liable to develop into the latter. It commences usually in the middle lobe, and spreads to the lateral lobes. It is rarely confined to the anterior lobe.

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[1] See footnote on p. 914 for record of this case.

[2] Henry Wade, "Prostatism," *Annals of Surgery,* March 1914, p. 321, Philadelphia, Penn.

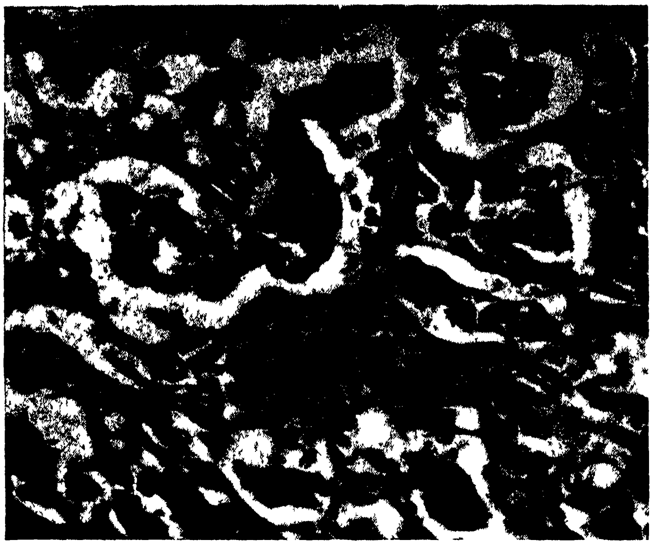

Fig. 541. *Metastasis in body of a cervical vertebra,* from same case as Figs 539 and 542 Hæmatoxylin and eosin × 400.

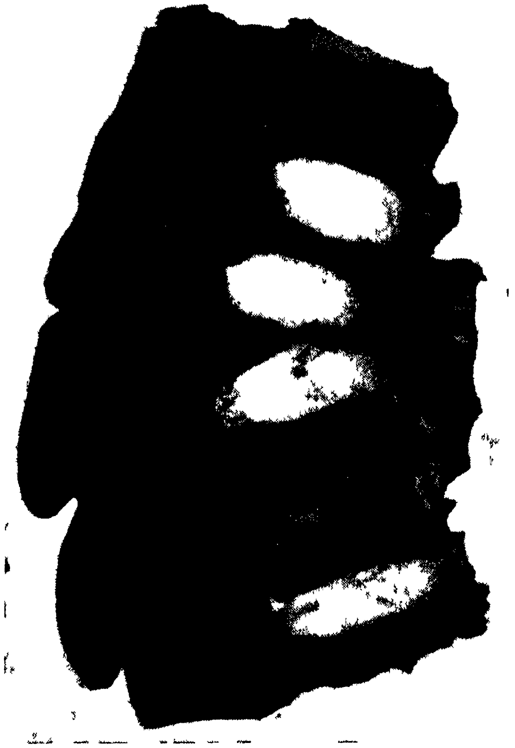

Fig. 542. *Metastases in the vertebral column from carcinoma of the prostate.* There is destruction and collapse of the bodies of the sixth cervical and first thoracic vertebræ, with approximation of the adjacent intervertebral disks and the formation of a bulge into the vertebral canal and compression of the cord (now removed). There are also extensive secondary growths of the tumour in the bodies of the sixth cervical vertebra above, and the second thoracic below, the region of the collapse. The patient was only thirty years of age, and during life there were no localising symptoms attributable to the prostate, which was not appreciably enlarged. (W.E.H. case.[1])

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[1] "Malignant Adenoma of the Prostate with Secondary Growths in the Vertebral Column simulating Pott's Disease," by Carnegie Dickson and Rowland Hill, *British Journal of Surgery,* 1934, **21,** 677.

(*b*) **Prostatic Fibrosis or Chronic Interstitial Prostatitis,** present in between 7 and 8 per cent. of the 134 cases examined. The gland is reduced in size, and shows sclerosis of the interglandular fibrous tissue, with dense adhesions to the capsule.

(*c*) **Prostatic Carcinoma,** the commonest true tumour of the gland, and found in about 10 per cent. of his 134 cases. The three types of carcinoma in his series were scirrhus, medullary cancer and adenocarcinoma. In Thomson Walker's series of 242 cases, 16·5 per cent. were malignant.

INFLAMMATION, or PROSTATITIS, may be **acute** or **chronic.** It is frequently due to **gonorrhœal** infection, especially where stricture supervenes, but may occur also as a complication of certain of the acute infective diseases. In gonorrhœa, the infection usually reaches the gland directly by way of the urethra, either naturally, or assisted by *urethral* injections or the passage of instruments. Streptococci, staphylococci and bacteria of the *Bacterium coli* type may be infecting agents, but more commonly they are secondary invaders and may be so numerous as to obscure the presence of gonococci. In some cases, abscesses develop, occasionally with thrombosis of the neighbouring veins, and sometimes pyæmia—a result which may also follow operative interference with the gland.

TUBERCULOUS DISEASE of the prostate is not infrequent, especially as part of the condition known as **Genito-Urinary Tuberculosis** (p. 72 *et seq.*). The urethra, vesiculæ seminales, etc., may be affected similarly.

TUMOURS AND CYSTS. Apart from the condition described above as hyperplasia, and which may sometimes closely resemble and merge into tumour-growth, neoplasms of the prostate are comparatively rare. **Fibromata** and **Myomata** may occur. **Carcinomas** constitute from 10 to 16.5 per cent. of carefully investigated series of prostatic cases operated on by the surgeon or examined *post mortem* (*see above*). The primary growth in the prostate may be small and, unless searched for carefully, may easily be overlooked. Carcinoma of the prostate gives rise to secondary growths in the lungs and in other organs, but not uncommonly they appear only in the bones, and a condition of osteosclerosis may develop round these secondary nodules, or, less commonly, erosion and softening (Fig. 542). In all cases of suspected tumour of the pelvic bones, vertebral column or spinal cord in the male, the prostate should be carefully examined as a possible and common site of the primary growth, the metastatic spread taking place by way of the prostatic venous plexus, sacral, vertebral and other veins (pp. 170–1). **Sarcomas** are uncommon. Small **retention-cysts,** often filled with colloid material, are of frequent occurrence, especially in chronic lobular prostatitis.

PROSTATIC CALCULI AND CONCRETIONS in the ducts of the gland are common in old persons. They are usually small in size, and are due, as a rule, to infiltration of inspissated mucus with lime-salts.

SECTION II

FEMALE REPRODUCTIVE ORGANS

In dealing with the pathology of the female reproductive organs, a knowledge of the physiology of puberty, menstruation, pregnancy, lactation, the puerperium and the menopause is essential, but, in order to understand some of the commoner pathological conditions, a brief outline of the main physiological facts will suffice. For full details readers are referred to textbooks of Physiology and Gynæcology or to special works on Endocrinology.

The occurrence of the menstrual cycle depends on the presence of certain hormones, derived from the anterior lobe of the pituitary—the gonad-stimulating hormones prolan A and B ; the former is the follicle-stimulating principle, the latter the principle concerned in the production of lutein. By their combined action they control the development of the reproductive organs. The Graafian (ovarian) follicles ripen, ovulation occurs and the corpus luteum is produced. As a result of the rapid maturation of the ovarian follicles, an œstrogenic substance (**œstrone, folliculin** or **theelin**) is produced from the cells of the membrana granulosa, and from the lutein-cells of the corpus luteum another substance, **progestin,** appears. The **œstrone** acts mainly by stimulating the development and functional activity of the genital apparatus. The **progestin** or **progesterone** is of special importance in both menstruation and pregnancy. It comes into action in the premenstrual stage, *i.e.*, immediately following ovulation and the production of the corpus luteum. In addition to its function of stimulating glandular activity in the uterine mucous membrane described on p. 917, it seems also to have an inhibitory action on the ripening of the ovarian follicles, for, if the corpus luteum survives, as it does in the early stages of pregnancy, no further maturation of fresh follicles takes place. If, on the other hand,

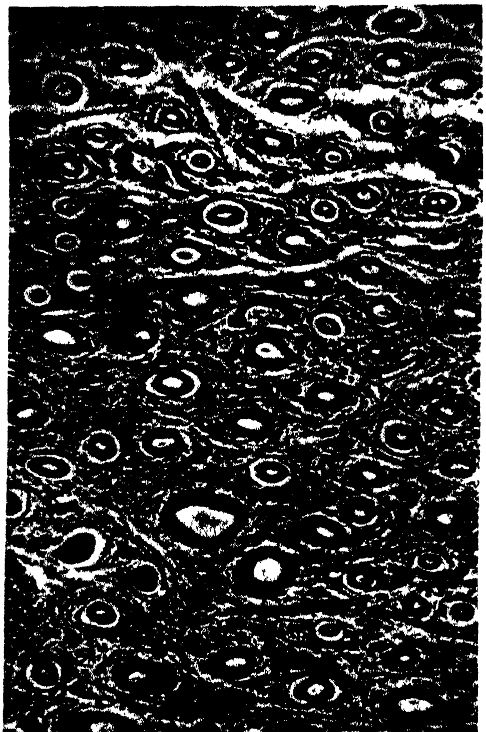

FIG. 543. *Menstrual cycle :* Section of curetting of uterine mucous membrane during *resting stage.* Note the regularity of the outlines of the glandular tissue. × 70.

its life is very short, as in ordinary menstruation, the stimulation of the ovarian follicles is resumed and ripening of fresh follicles continues.

In this premenstrual stage, increased glandular activity and increased secretion on the part of the uterine mucous membrane is observed. The glands become distended with mucus and their epithelial lining is thrown into folds; the superficial layer of the membrane becomes dense, whilst the deeper part is spongy, with irregular and tortuous glands. The stroma-cells of the compact layer swell, become rounded or ovoid in shape and have some resemblance to decidual cells. This **decidual reaction** of the premenstrual stage is similar to, but much less marked than, that of pregnancy. The capillaries of the stroma become congested and, with the onset of menstruation, leucocytes appear, hæmorrhage into, and necrosis of, the mucous membrane take place, the compact layer is cast off, the walls of the capillaries are destroyed and blood escapes into the uterine cavity and thence through the vagina to the external surface. The menstrual flow consists of blood, migrated leucocytes, mucus and necrosed mucous membrane. Later, the blood extravasated into the stroma is rapidly absorbed, the epithelium is regenerated, and the mucous membrane is restored to its normal condition. If the ovum has been fertilised, enlargement and continued activity of the corpus luteum follows, the menstrual cycle ceases, and the mucous membrane of the uterus develops into the decidua (Fig. 547),

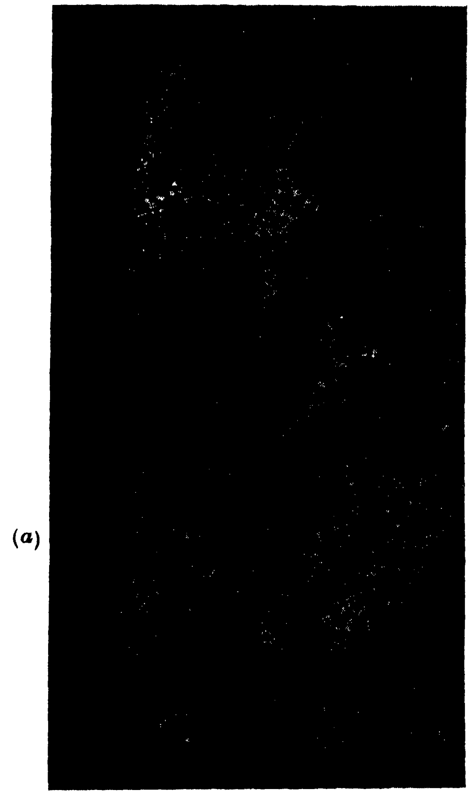

FIG. 544. *Menstrual cycle:* Curetting of uterine mucous membrane during the *premenstrual* (*lutein*) *stage*. Note the proliferation of the glandular tissue, the papilliform processes and the irregularity of the outlines of the glands. The stroma is cellular, but at one area (*a*) the cells are arranged in a concentric fashion, tend to be spindle-shaped and resemble the decidual cells (compare Fig. 547). × 70.

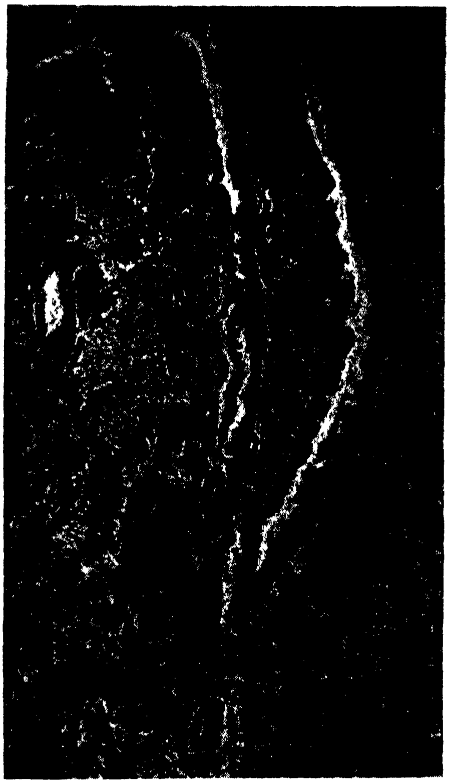

FIG. 545. *Menstrual cycle:* Curetting of uterine mucous membrane during the *proliferative* (*premenstrual or lutein*) *stage*, showing the increased and irregular glandular elements, and especially the cellular and hæmorrhagic stroma on the left of the illustration. × 50.

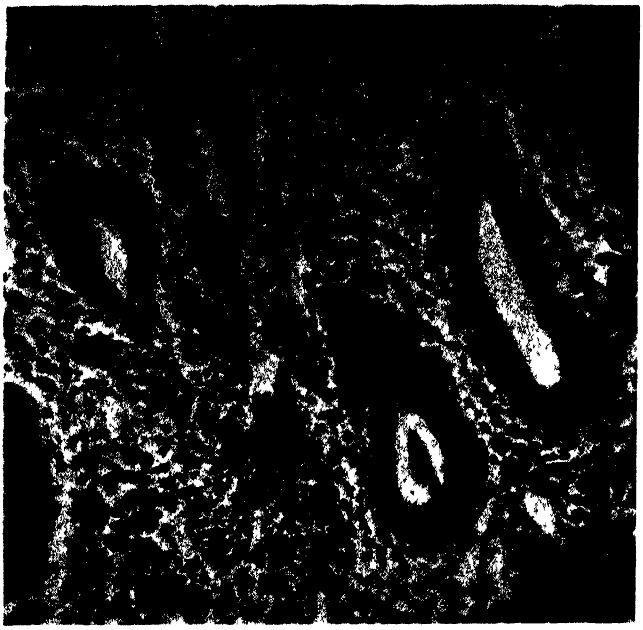

FIG. 546. *Menstrual cycle:* Section of curetting from the uterine mucous membrane in the *post-menstrual stage—the reparative phase.* Note the regular outline of the glands and the denser, spindle-celled character of the stroma. × 120.

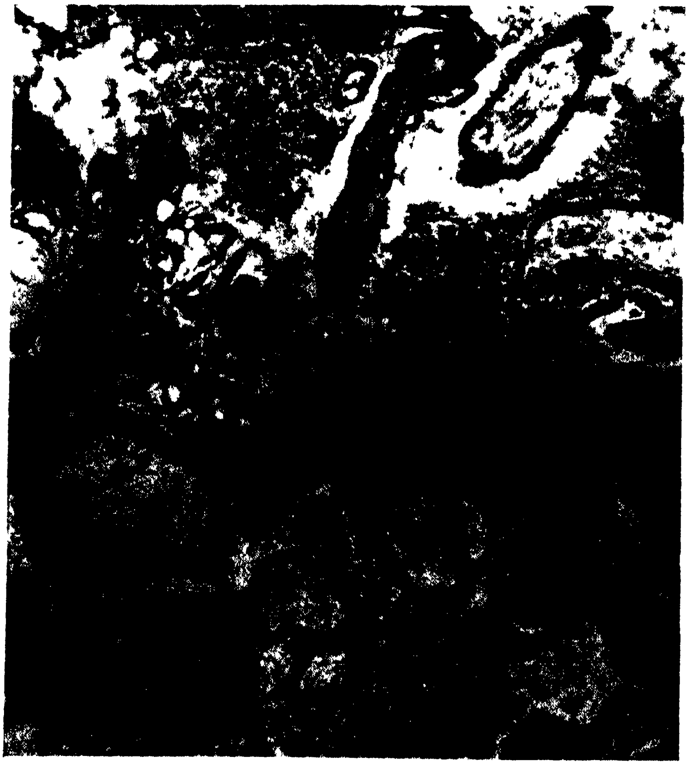

FIG. 547. Section of curetting of uterus—*shortly after pregnancy*—showing decidual cells and remains of chorionic villi. Compare with Fig. 544. × 70.

in which the fertilised ovum becomes embedded. It may be assumed, therefore, that the formation of the decidua of pregnancy, the inhibition of ovulation and the amenorrhœa during the period of pregnancy are all due largely, if not wholly, to the action of the **lutein** secretion—progestin—from the specially-active corpus luteum of pregnancy. It is possible that this activity is maintained by some substance produced by the implanted ovum and the developing placenta, and it is known that, **in the placenta** and **in the urine** during the active period of pregnancy, a substance similar in action to the gonad-stimulating hormone of the anterior lobe of the pituitary is present, and it is this substance which is active in the Aschheim-Zondek and other analogous tests.

Further ovarian follicles do not ripen during the early stages of pregnancy and, as a result, the supply of the œstrogenic substance is limited, but this ripening is resumed in the later stages and the œstrone again becomes active. The œstrogenic substance is concerned in the enlargement and proliferation of the breasts and their preparation for lactation. When pregnancy terminates and complete evacuation of the placenta has occurred, the Aschheim-Zondek test at once becomes negative, but, if placental tissue is retained or if the condition of " hydatid mole " develops, the test remains positive.

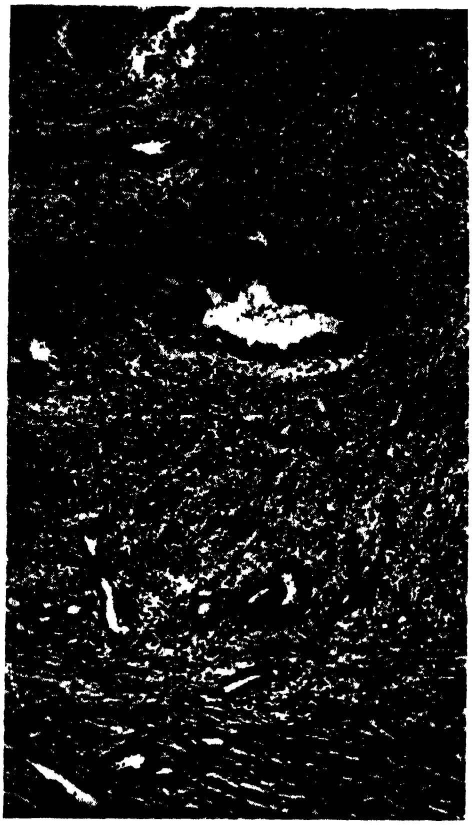

FIG. 548. Section of curetting of uterine mucous membrane *after the menopause*. Note that the glandular elements are now very scanty and the stroma fibro-cellular. New vessels are seen in this organising fibro-cellular tissue. × 70.

Considering the uterine reactions which are associated with the premenstrual and menstrual periods, it is not unreasonable to assume that some of the conditions which have been described under the terms " glandular endometritis," " hypertrophic endometritis " and " atrophic endometritis " are really physiological processes or the exaggeration or abeyance of these. Uterine hæmorrhage during the menopause and at other periods of sexual life may also result from abnormal ovarian function. The influence of the pituitary as the " master-gland " presiding over many of the activities of the endocrine system is referred to on pp. 806–8.

THE UTERUS

ENDOMETRITIS AND ENDOCERVICITIS

Acute Endometritis. Acute inflammation of a previously normal uterus is uncommon and, though it may occur as a result of mechanical interference and in some infective fevers, its commonest cause is an infection with the organism of gonorrhœa, and in such cases the condition is usually confined to the cervix (**endocervicitis**). In a few cases, the infection spreads by way of the uterine cavity to the uterine (Fallopian) tubes, causing a salpingitis, sometimes without evident infection of the uterus itself. Generally, however, if a spread to the uterine mucous membrane takes place, the subjacent muscle is infected and the condition is apt to become chronic. In the pregnant, and in the puerperal, uterus, especially if portions of placenta are retained, acute infection is not uncommon and may cause severe and widespread lesions. Bacteria of several types are causal in different cases, but *Streptococcus hæmolyticus* is generally regarded as the organism mainly concerned in this infection. In gonorrhœal infections the cervix is swollen, the external os is surrounded by a zone of congestion, and purulent secretion may be abundant in the upper part of the vagina. In the forms occurring in infective fevers and especially in the puerperal type, the lesions vary considerably. There may be swelling and congestion of the mucosa, with desquamation of the epithelium and sometimes hæmorrhage; but, in "**puerperal fever,**" a fibrinous exudate is deposited on the uterine mucous membrane, with superficial necrosis and ulceration; or the uterus may be enlarged, soft and flabby, and its cavity lined with breaking-down blood-stained necrotic tissue. This tissue and the subjacent muscle of the uterus are invaded by leucocytes, mainly of the polymorphonuclear type.

The organisms may spread along the lymphatics to the pelvic connective tissue or by way of the uterine tubes, giving rise to salpingitis and oöphoritis or peritonitis. These are not uncommon complications in gonorrhœa. In the puerperal state there may be a spreading lymphangitis, producing inflammatory œdema and suppurative foci at various situations or septic thrombosis of the venous sinuses of the uterus, especially of those at the placental site, and a spread from these to the iliac veins. The thrombi may undergo suppurative softening and the septic emboli may give rise to pyæmic abscesses, especially in the lungs. Sometimes, however, there is an invasion of the blood-stream by the streptococci and death from septicæmia.

"**Chronic Endometritis.**" Reference has already been made to the proliferative and atrophic changes in the uterine mucous membrane, which were at one time regarded as the results of inflammatory reactions. These are now generally recognised as being due to stimulation by the œstrogenic substances derived from the ripening ovarian follicles and the progestin from the corpus luteum. This stimulation may be deficient or in excess of the normal, and in consequence pathological results follow. Excessive hyperplasia and hypertrophy of the glandular tissue may occur. The endometrium is thickened and shows polypoidal projections on the surface. The glands are irregular in shape and size, may be dilated and produce cysts, and they may invade the muscle-fibres of the uterus, especially where there are associated "fibroids" in the uterine wall. The stroma of the mucous membrane is cellular and very vascular, and bleeding is common. Patchy necrosis of the superficial layers and infiltration with polymorphonuclear leucocytes frequently occur and are associated with irregular uterine hæmorrhage in women about the age of forty to forty-five, constituting the state known as **metropathia hæmorrhagica.** It is suggested that the hyperplasia in such conditions is due to a persistent ripening of the ovarian follicles and therefore an uninterrupted action of the œstrogenic substance. This results from a failure in the production of progestin, or, it may be a failure of its inhibitory power, and the degenerative, which follow the proliferative, changes, in normal menstruation are largely in abeyance. The menstrual cycle is incomplete. The ovaries in such cases frequently contain cysts and usually no corpus luteum is present.

A true **chronic endometritis,** usually of the atrophic variety in which there is thickening and contraction of the interstitial tissue with atrophy of the glands, may occur in connection with displacements of the uterus, and as a result particularly of gonorrhœal infections. Various degrees of thickening and fibrosis are seen in different cases. In the early stages, the proliferating connective-tissue cells and newly-formed capillaries are present ; later, the tissue is more fibrous and collections of lymphocytes and plasma-cells are seen infiltrating it. The contraction of the newly-formed fibrous tissue may lead to stenosis of the os and partial obliteration of the uterine cavity. In the infected cases, a thick muco-purulent discharge from the racemose glands may be a marked feature. This chronic infection is commoner in the cervix than in the body of the uterus and may be associated with lacerations produced during child-birth and which have remained unhealed.

Cervical " Erosions." These are generally secondary to catarrh of the cervix and the constant irritation which results from the infected leucorrhœal discharge. The squamous epithelium round the external os degenerates and becomes eroded. This denuded surface becomes covered with a new layer of columnar epithelium, which is an extension over it of the epithelium lining the glands in the wall of the vaginal portion of the cervix, or a metaplasia of the mucous membrane lining the cervix itself. The affected area looks red and raw. Associated with the catarrh of the cervix, cystic dilatations in the region of the os are common. These so-called "**Nabothian follicles**" are due to the closure of the orifices of the cervical glands by the new formation of tissue and especially the new squamous epithelium produced during the process of healing. The cervix becomes hard, owing to the fibrosis in its deeper parts ; and the contraction of the newly-formed connective tissue sometimes causes eversion of the lips of the os. Carcinoma may be a sequel of the chronic irritation.

TUBERCULOSIS. Primary tuberculosis of the endometrium is rare and, if tuberculous infection is present, it is practically always only part of wide-spread tuberculosis elsewhere.

TUMOURS. Polypi are common and may be single or multiple. They are usually small and grow from the mucous membrane of the body of the uterus or of the cervix. They are composed of a core of vascular connective tissue covered by a layer of epithelium characteristic of the mucosa of the uterine body or of the cervix. Many of these are merely polypoid masses of the hypertrophied mucous membrane resulting from irritation, and not true neöplasms. The cervical growths may project through the external os into the vagina. In such, especially if present for a considerable time, the covering cells may be in part squamous epithelium. This is probably a metaplastic change in the original columnar-celled coating covering a damaged surface, rather than a proliferative spread of the epithelium from the lips of the external os or from the vagina. In some of these polypi, the glandular tissue extends into the stroma and there produces an adenoma-like appearance. Such projections may be attached to the uterus by a pedicle and hang free in the cavity. They may give rise to hæmorrhage and often become the seat of septic infection and necrosis.

Myoma (Leiomyoma) (Figs. 145 to 148, pp. 311 to 313). These tumours are common in the uterus, and are composed of fasciculi of non-striped muscle-fibres, supported by a varying amount of fibrous tissue, together with its blood-vessels. They may be confined to and enclosed within the muscular wall of the uterus (**interstitial form**) ; may project into the cavity and perhaps become pedunculated (**submucous form**) ; or may grow outwards and project from the peritoneal surface (**subperitoneal form**) (Fig. 148). The muscle-bundles are usually arranged in a whorled or concentric manner and the amount of fibrous tissue varies considerably in different specimens. Where the fibrous tissue is abundant, the term "**fibro-myoma**" is applied. The tumours are usually multiple and the submucous variety may expand the uterine cavity and come to project through the os. Usually, the tumours are firm and elastic in consistence and the whorled arrangement of the fibres is generally very evident. The tumour may become œdematous ; hyaline and fatty degeneration and mucinoid softening are sometimes present ; and necrosis with hæmorrhage—**red degeneration**—may occur, possibly from thrombosis of the vessels or congestion due to strangulation from twisting of the pedicle. Reduction in size often takes place after the menopause, the muscle becomes considerably reduced in amount and the fibrous tissue relatively increased. Deposits of lime-salts round the periphery or a varying degree of interstitial calcification is not uncommon, and in some cases the whole tumour is converted into a hard stony mass (womb-stone). Occasionally, a sarcomatous transformation takes place, probably starting in the muscle-cells.

Adenomyoma. Endometrioma (Fig. 549). Nodular masses, indefinite in outline and composed of glandular tissue, non-striped muscle and connective-tissue, are frequently found in the uterine wall, especially at the area where the uterine tubes enter, in the tube itself, as well as in the ovaries, the vaginal wall, the broad ligament and elsewhere in the region of the pelvis. These, **on microscopical examination,** show gland-like tubules or cavities, irregular in shape, lined by columnar epithelium and surrounded by a comparatively cellular tissue. They are scattered among the smooth muscle-fibres, and, in their general appearance, suggest fragments or patches of uterine mucous membrane. These were described by von Recklinghausen as "adenomyomas" and were regarded by him as tumours developing in misplaced remnants of the Wolffian duct. They are now generally considered to be due to invasion of the muscular tissue by prolongations of the endometrium which have been cut off from the parent tissue and which, in their abnormal situation, have taken on active growth and function. This origin is borne out by the fact that they participate in the menstrual phenomena; they swell, and hæmorrhage may take place into or from them. Further, during pregnancy, cells resembling decidual cells are found in the characteristic cellular zone which surrounds these glandular acini.

Other more circumscribed nodules, which may be submucous or subperitoneal, often cystic in character, are sometimes found. These are composed of enlarged and distorted uterine glands embedded in cellular connective tissue. Though sometimes called adenomyomas, they are in reality adenomas, but it is sometimes difficult to differentiate between these two types of growth (p. 314).

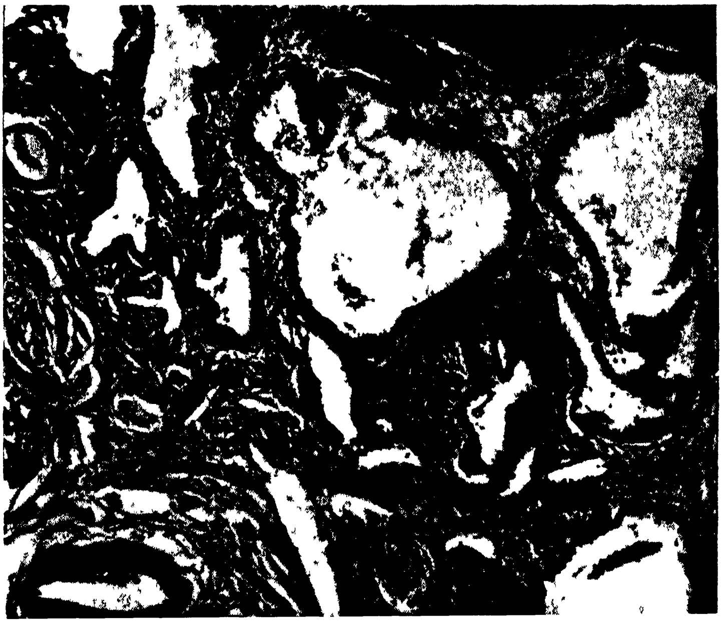

FIG. 549. *Endometrioma of the broad ligament.* Note the irregular gland-like structure —the spaces are lined with columnar epithelium and the stroma is cellular. × 75.

Carcinoma. This growth may occur in the **cervix** or in the **body** of the uterus. The **cervical form** is the commoner and often arises in association with lacerations or erosions of the cervix. For this reason it is commoner in women who have borne children, and commences usually about the menopausal period or between the ages of forty-five and fifty. The growth, in the majority of instances, takes origin from the squamous epithelium of the vaginal portion of the cervix, and appears at first as an indurated and possibly ulcerating area. The wall of the cervix is invaded at an early period and lymphatic spread to the neighbouring tissues is also an early manifestation. The regional lymph-nodes are invaded, and, in the later stages, extensive destructive changes take place. The cervix may be eaten away, the vagina, the bladder and the outlets of the ureters involved, and there may be a spread into the body of the uterus.

Microscopically, the growth appears as solid, irregular groups or masses of epithelial cells invading the tissues. Cell-nests are seldom present. The character of the proliferated epithelium and the absence of cell-nests in the majority of cases has suggested that the basal layers of the stratified epithelium are the progenitors of the cells of this tumour. Occasionally, the growth has the character of an adenocarcinoma, and the site of origin is then probably either the lining-cells of the glands of the cervical canal or squamous epithelium which has undergone metaplasia and been converted into a cubical-celled type. This metaplasia is sometimes seen in the epithelium covering an erosion (p. 921).

Carcinoma of the body of the uterus is of rather less frequent occurrence than cancer of the cervix, and is usually of the adenocarcinomatous type. It may form an irregular ulcerated nodular mass, or may be more diffuse, infiltrating the wall of the organ. It is one of the causes of uterine hæmorrhage after the menopause, and is much more radio-resistant than the commoner cervical type of tumour.

Sarcoma of the uterus is comparatively rare. It may arise from the stroma-cells of the mucous membrane, but many authorities regard it as a malignant transformation of the muscle-cells of the uterine wall or of the muscle-cells in a myoma. The cells are usually of spindle-type, but tumours composed mainly of round or of mixed cells do occur.

Hydatidiform Mole [1] and **Chorionepithelioma** (*see also* p. 352). Though these lesions are really pathological changes in the placenta, it is convenient to deal with them among uterine tumours. During pregnancy, there is normally a downgrowth of the chorionic villi into the wall of the uterus. Usually, this invasion gives rise to no pathological condition, and the invading villi are destroyed when pregnancy is over. Sometimes, however, during pregnancy the chorionic villi both in the uterine wall and in the placenta itself undergo a curious development and the whole of the placenta is converted into a loose villous mass resembling clusters of cysts or bunches of grapes (Fig. 191, p. 352). These soft masses are swollen and enormously enlarged chorionic villi covered with epithelium. Towards the termination of pregnancy, this " mole " may be expelled from the uterus, either with no fœtus or only its imperfect remnants. The invasive part of this growth may disappear ; but, in some instances, it gives rise to invasive malignant tumour-masses and metastases, especially in the lungs.

When these hydatidiform moles (so called because of their resemblance to masses of cysts of *Echinococcus* larvæ (hydatids)) assume malignant characters, the tumour produced is a **chorionepithelioma** (p. 352) which may also take its origin from chorionic villi of a normal placenta, especially those which become embedded in the uterine wall. Such malignant tumours may interrupt pregnancy or may develop several months or even, in a few cases, several years after a pregnancy or miscarriage. The tumour is a soft, intensely hæmorrhagic mass, varying in colour from grey to brown, depending on the degree of necrosis and deposition of blood-pigment. It causes absorption of the uterine wall and may penetrate to the peritoneum. The tumour-cells tend to enter the veins, and metastases similar in character to the primary growth are common in the lungs, but may also occur in the vaginal wall, brain, liver and lymph-nodes—the latter

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[1] " Mole," from Latin, *mōles*, *-is*, f., a mass, here applied to a " mass " formed in, and discharged from, the cavity of the uterus, as the result of the arrested development or degeneration of an ovum, *cf.* " blood-mole," " false mole," etc. To be distinguished from " mole," a spot or blemish on the skin, from Old English, *mál* (from Latin macula ?), a spot.

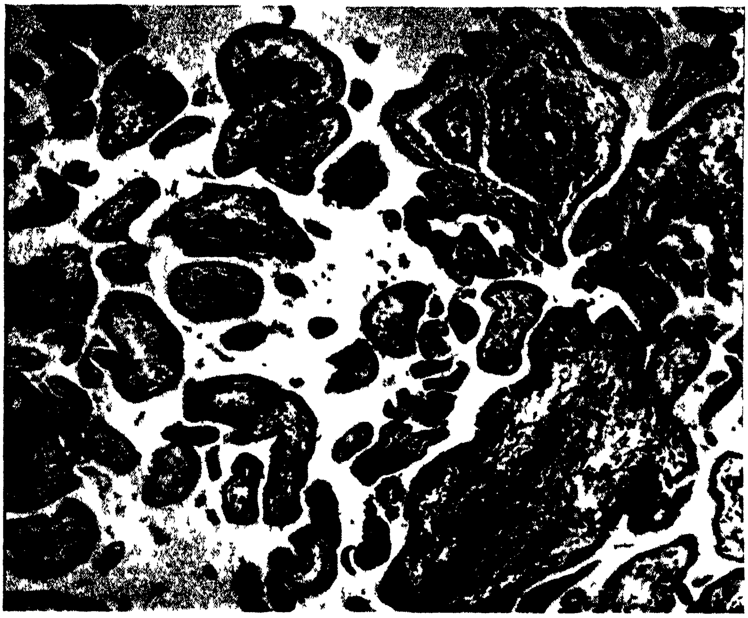

FIG. 550. *Uterine curetting section showing chorionic villi* The dark outline indicates the now considerably thinned *syncytial trophoblast* covering the subjacent *cellular trophoblast layer of Langhan's cells,* which in turn surrounds the cores of the villi, some of which are becoming fibrosed Hæmatoxylin and eosin. × 70

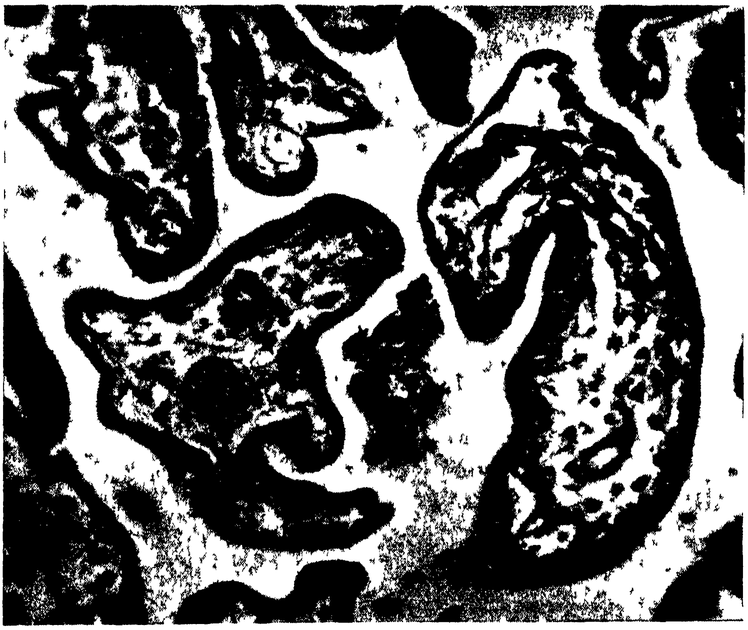

FIG. 551. *High-power view of the same specimen,* showing the darkly-stained multinucleated *plasmodial* or *syncytial trophoblast* forming a thinned covering over the now atrophied and disappearing subjacent *cellular trophoblast* (*Langhan's layer*), surrounding the loose vascular mesodermal cores of the villi [1] Hæmatoxylin and eosin. × 300.

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[1] *Cf.* Schafer's "Essentials of Histology," 14th edition, 1938, edited by H. M.Carleton, "Structure of the Placenta," p. 444.

situation suggesting a spread by lymphatics as well as by the blood-stream. Teacher (1907) showed that the secondary nodules in the lungs may undergo a process of retrogression and healing, especially after the removal of the primary uterine tumour.

The tumours are composed almost entirely of the two types of chorionic epithelium—the Langhan's cells, which are small, rounded or polygonal with a pale or almost clear cytoplasm and fairly sharp cell-outline, and the syncytial trophoblastic layer which spreads over the Langhan's layer as multinucleated protoplasmic masses. The syncytial cells stain more deeply than the Langhan's cells. The stroma is scanty and consists of œdematous and myxomatous tissue from which blood-vessels seem to be entirely absent (Figs. 550–1, p. 925).

In a considerable proportion of cases, both of hydatidiform mole and chorionepithelioma, the ovaries are enlarged and contain many cysts resembling lutein-cysts, and it is suggested that the overgrowth of the chorionic villi is due to an over-stimulation by the increased amount of corpus-luteum hormone. The urine, as a rule in both conditions, gives a positive Aschheim-Zondek reaction ("A.Z.R.") and this becomes negative if the growth is removed.

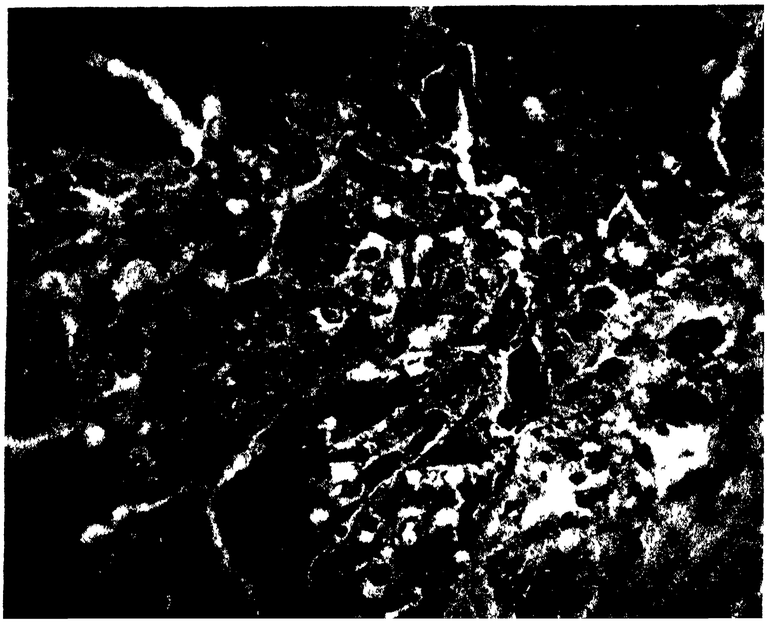

FIG. 552. *Chorionepithelioma*, secondary growth in lung : showing the smaller cells with definite cell-outline and single nucleus (Langhan's cells) : and the irregular plasmodial masses, usually multinucleated (the syncytial trophoblast-layer). × 310.

THE UTERINE (FALLOPIAN) TUBES

Acute Salpingitis or inflammation of the tubes is, in at least 80 per cent. of cases, due to infection with gonococci—the remaining 20 per cent. being caused by other pyogenic cocci, especially streptococci. The infection is usually of " ascending " type, extending upwards from the uterus. Occasionally, the infecting bacteria enter from the peritoneal cavity through the abdominal **ostia** or distal openings of the tubes into the cavity. The inflamed tubes may develop only a catarrh of the mucous membrane, with some cellular infiltration of their walls ; but, not uncommonly, suppuration takes place and one or both of the tubes may become distended with pus. More rarely, a fibrinous deposit on, and necrosis of, the mucous membrane occur. The inflammatory reaction frequently extends to the ovaries and to the serous surface of the tubes themselves, with the production of adhesions between the tubes and the surrounding tissues and perhaps blocking of one or both abdominal ostia. The tubes become dilated and form irregular, elongated sausage-shaped swellings filled with pus—**pyosalpinx.** Later, the pus may become inspissated and the walls of the tubes infiltrated and thickened, and in such conditions the infecting organisms may be difficult to find or may have disappeared. In less acute cases, the exudate into the tubes may be serous ; and sometimes a chronic salpingitis develops without obvious symptoms of suppuration. Eroded areas of the mucous membrane may come in contact and be united by granulation-tissue, and adhesions may be formed around the tube, giving rise to local dilatations in which collections of serous or purulent fluid are found. Hæmorrhage may occur into these pockets, or into the lumen of the tube, the condition being then known as **hæmatosalpinx.**

Tuberculous salpingitis is commonly bilateral and is in most instances hæmatogenous in origin. Rarely is there a direct spread from abdominal tuberculosis. Tubercles are formed on the tubal mucosa, and these undergo ulceration and necrosis. The lumen becomes filled with caseous material and the walls greatly thickened. Adhesions are formed between the tubes and adjacent structures, the ostia become blocked, the tubes dilated and a condition of **tuberculous pyosalpinx** is produced. Infection may spread from the tubes to the peritoneum, either by direct passage through their walls, in which numerous tubercles are seen, or by way of the abdominal ostia.

Tumours. These are relatively rare. Benign fibromas, myomas and adenomas occur, and both carcinomas and sarcomas are occasionally found. Chorionepithelioma as a sequel to tubal pregnancy has been recorded.

THE OVARIES

OÖPHORITIS (" Ovaritis ") or INFLAMMATION. Reference has already been made to the spread of acute inflammation from the uterine tubes. Infection may take place also from the peritoneum in appendicitis or other infections of the intestine. In all cases, a serous or fibrinous exudate is present, and sometimes suppuration follows, the pus being diffuse : or localised to abscesses in the follicles—**lutein-abscesses.** In the more chronic conditions, it is often difficult to estimate how much of the fibrosis is secondary to inflammatory changes and how much is due to the normal reactive changes around the corpora lutea. Oöphoritis sometimes occurs as a complication of mumps (p. 117).

TUBERCULOSIS is uncommon and is usually secondary to uterine-tube infection.

CYSTS and **TUMOURS.** These may be derived from the capsular epithelium, the membrana granulosa, the lutein-cells, the endothelium of lymph-vessels and blood-vessels, from glandular tissue and from the connective-tissue stroma.

Cysts: Follicular Cysts. These may be distended ovarian follicles or lutein-cysts. They are usually unilocular, and the former especially may be very numerous. In size they vary considerably, but generally are small and the contents are usually a clear serous fluid. They may contain blood and form a hæmatoma. Those derived from the ovarian follicles have a smooth fibrous wall and are lined by a cubical or columnar epithelium. The corpus-luteum cysts may show a thick layer of lutein-cells which are rounded or polyhedral in shape and contain fatty material and yellowish pigment. Sometimes there are only a few lutein-cells present.

The follicular cysts are in some cases the result of chronic inflammation in the ovary, and distension of perivascular spaces from accumulation of fluid, but they are also said to be formed by ingrowths of the surface germinal epithelium into the ovary.

"Tarry" or "Chocolate-Cysts." In this form of hæmatoma, a tissue resembling endometrium is always present. These cysts are described under endometriosis (pp. 922–3 and 929).

Multilocular or Compound Ovarian Cysts (Figs. 160–1, pp. 327–8) (Cyst-adenoma or pseudomucinous cystadenoma). This cystic tumour is generally unilateral, spherical or ovoid in shape, smooth on the surface and contains numerous cysts of which one is usually specially large. At one side of this main cyst, there is a more solid-looking mass composed of innumerable cysts of varying size. The contents are mucinoid in character and sometimes almost semi-solid.

On **microscopical examination,** the cysts are seen to be lined by a tall columnar epithelium; the nuclei are deeply placed and the cytoplasm is clear because of its mucinoid character. There may be few or numerous papillary projections into the cyst. The stroma is well-formed connective tissue. Torsion of the pedicle is common in mobile ovarian cysts. If this is sudden and complete, the blood-supply is entirely interrupted and necrosis supervenes. If the torsion is gradual, hæmorrhages take place into the cyst, and the tumour becomes a dark plum-colour. The cyst may rupture and its mucinoid contents escape into the peritoneal cavity. Reactive changes follow and adhesions between the coils of intestine and other structures are formed, producing cyst-like spaces which are filled with mucinoid material. This condition is sometimes described as **pseudomyxoma peritonei.** According to Blair Bell, malignant changes supervene in about 12 per cent. of the cases.

Papillomatous Cysts. These are frequently bilateral. The papillary or wart-like growths, which may be very numerous, arise inside the unilocular cyst and may subsequently break through and become implanted on the surrounding peritoneum. Microscopically, the papillary projections, which arise as a proliferation of the lining-epithelium, have a delicate stroma and are covered usually by a single layer of columnar or cubical epithelium. Some of these tumours are malignant, but often only a careful consideration of the clinical history and histological examination of various parts of the tumour will enable a correct diagnosis to be made.

Teratomas (pp. 291 and 351). The commonest of these are the so-called "dermoid" cysts which are sometimes bilateral. The main cyst-wall is thick and fibrous, and smaller cysts, if present, are lined mainly by stratified, usually squamous, epithelium. The contents are composed of sebaceous material, hair, skin, teeth and bone, etc.,—*i.e.*, usually mainly, but *not* exclusively, ectodermic structures. Occasionally, epithelium resembling that of chorionic villi is present.

The mixed-tissue solid teratomas are ovoid tumours with an irregular surface. Microscopically, the growth shows epithelial and connective tissue arranged in no apparent order. They are always malignant, grow rapidly and produce metastases.

Endometriosis. Small nodules, similar in histological structure to the endometriomas found in the uterus, occur in the ovary. These are sometimes present as cysts containing a dark-reddish fluid resulting from hæmorrhage into this aberrant endometrial tissue during menstruation ("**chocolate-cysts**"). It is not necessary to discuss the various views as to how this endometrium reaches the ovary, but it is commonly accepted that an implantation of the endometrium, shed during menstruation, can be deposited at first on the surface of the ovary and later give rise to the formation of endometrial areas in the ovarian substance. Each patch undergoes menstrual changes. The chocolate-cysts so formed may become densely adherent to the surrounding structures. Malignant development may occur, leading to adenocarcinoma.

Similar endometriosis has been observed on the peritoneal surface in the lower part of the abdomen and in the walls of the vagina. Portions of endometrium are sometimes found within the uterine tubes, and it is known that menstrual blood may escape into the peritoneum from the fimbriated end of the tube.

Of the solid, **non-malignant tumours,** fibromas and fibro-myomas are the commonest. They are composed of closely arranged connective-tissue cells and fibres or of smooth muscle with a fibrous stroma. They may become papillomatous. Some of the papillomatous growths in the ovary contain glandular tissue and may be regarded as adenomyomas, or endometriomas. They sometimes show cystic formation, with hæmorrhage into the cysts.

Sarcomas of the ovary are uncommon, and when present are usually of spindle-celled or mixed-celled variety.

Carcinomas of the ovary may be primary, or may be secondary to mammary, gastric or intestinal carcinoma. **Primary** tumours occur not infrequently in both ovaries simultaneously. They may be hard, with cells arranged in groups as in the scirrhous type : or soft and friable, the cells having an acinous formation and somewhat aberrant character. Some are associated with, and possibly arise from, papillomatous growth or from cystadenoma. Metastases from these may be confined to peritoneal implantations and give rise to hæmorrhagic ascites or, in other cases, may be widely disseminated in the regional lymph-nodes, liver and possibly other organs. **Secondary** growths are comparatively common, nearly always bilateral and may develop rapidly.

A bilateral tumour in the ovary in which cancer-like cells, in masses or more scattered, lie in a cellular matrix, has been described by **Krukenberg** (pp. 349 and 730). The cells contain mucinoid material, and the nucleus is often seen at the periphery of the cell—pushed aside by the accumulation of the mucinoid contents (p. 349). The tumour is now generally regarded as a **metastatic growth of carcinoma**—the primary tumour being in the stomach, the intestinal tract or possibly in the breast.

Granulosa-cell Tumours (Figs. 553 to 556). These are supposed to arise from masses of granulosa-cells which are occasionally seen in the ovary, but unassociated with the cells of the ovarian follicles. The tumour may occur at any age. It is œstrone-producing, and is probably of primitive ovarian-follicle-cell origin. Rarely, it assumes a cystic type, but is usually firm in consistence and composed of rounded or polyhedral cells arranged in solid masses or sometimes in an alveolar fashion and resembling a carcinoma. Small spaces, empty or containing homogeneous material (the so-called " Call-Exner spaces " illustrated in Figs. 553 and 554) are scattered throughout the tumour-cell masses. Round these spaces. and also outlining the larger cell-aggregates, a radiate arrangement of the tumour-cells is a distinctive feature. According to Ewing, characteristic ova-like cells—the " Call-Exner bodies " (Figs. 553–4)—are present. These result from hydropic degeneration of cells and form minute clear spaces around which the other cells are grouped in rosette-fashion. In other specimens, the arrangement is more diffuse—" sarcomatous " in appearance—

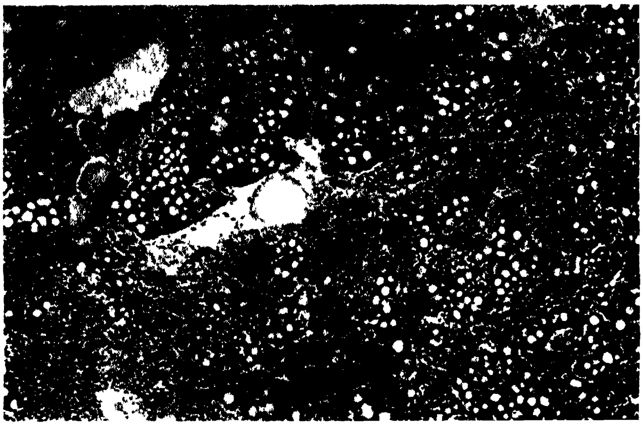

FIG. 553. *Granulosa-cell tumour* a " folliculoid " tumour from a girl aged eleven, who menstruated at the age of nine. Islets and strands of the tumour-cells are shown, containing the characteristic " organoid " spaces (of " Call-Exner " type). These spaces may fuse and coalesce (as shown towards top left corner). × 40.

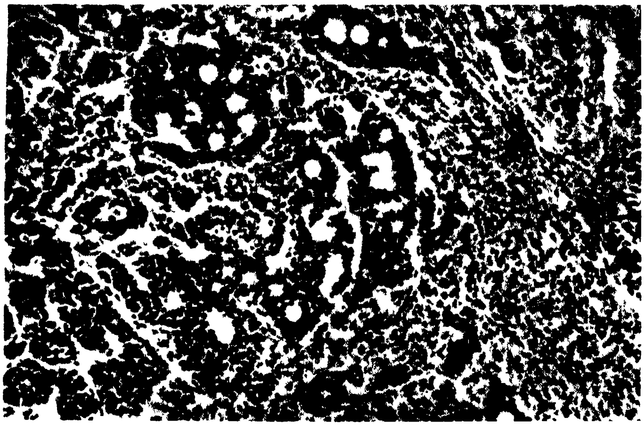

FIG. 554. *Granulosa-cell tumour :* higher power of the same showing the grouping of the " folliculoid " tumour-cells. × 150.

and the tumour is well supplied with capillaries. Though the tumours are generally unilateral and of low malignancy, metastases have been observed in about 10 per cent. of cases. When the tumour occurs in young children, it is associated with a premature puberty (Fig. 553)—unduly early menstruation, abnormal development of the breasts and an abundant growth of hair. If it develops during the child-bearing period, or, as is commoner, later in life, after the menopause, the effects are enlargement of the uterus, hyperplasia of the endometrium and periodic uterine bleeding—"**pseudo-menstruation.**" These reactions suggest that the cells produce an œstrogenic substance which gives rise to hyperplasia of the endometrium and to the premenstrual phenomena. Removal of the tumour causes the disappearance of the symptoms.

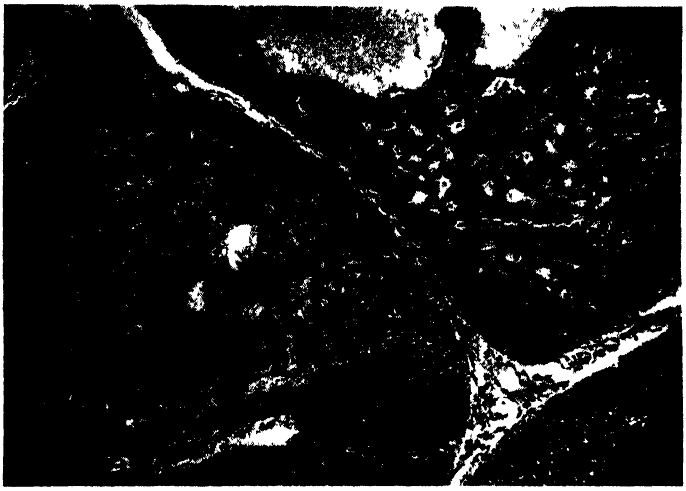

FIG. 555. *Granulosa-cell tumour* : showing two characteristic folliculoid masses, bordered by radially arranged cells, associated with hyperplastic cystic endometrium. × 80.

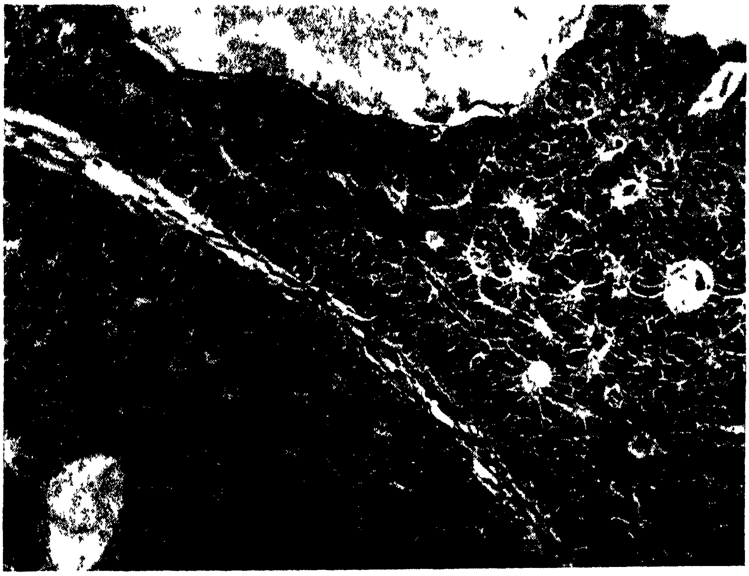

FIG. 556. *Granulosa-cell tumour* : high-power view of the same section to show the characteristic radiate arrangement of the cells and their columnar form. (Figs. 553 to 556 are by courtesy of W. F. Harvey, E. K. Dawson and J. R. M. Innes, Research Laboratory, Royal College of Physicians, Edinburgh.) × 150.

Arrhenoblastoma.[1] This variety of ovarian tumour, which takes its origin from cells in or in the region of the rete ovarii—the homologue in the female of the testis—leads to the production of secondary male characters in the woman. There is atrophy of the breast and uterus. There may be the growth of a beard, enlargement of the clitoris and the production of a deep-toned voice. Excision of the tumour removes these symptoms. The cells in this tumour have a somewhat tubular grouping and though the majority are of the round-celled type, here and there larger cells with abundant cytoplasm containing slightly eosinophil granules are found. No œstrogenic substance is present and no substance inhibiting ovarian function has been demonstrated. The reaction on the individual is somewhat similar to that which occurs in some tumours of the adrenal cortex (p. 847).

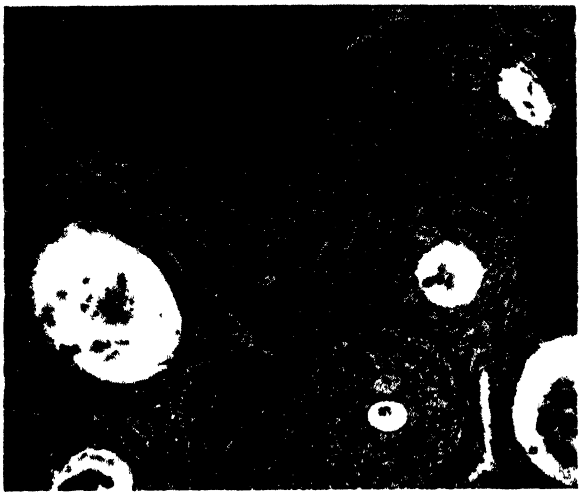

FIG. 557. *Brenner's tumour or "oophoroma folliculare"*: showing solid and cystic alveolar masses embedded in hyperplastic ovarian stroma. × 80.

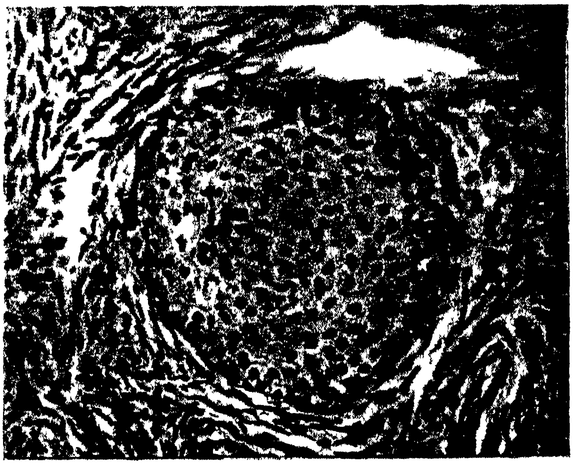

FIG. 558. *Brenner's tumour or "oophoroma folliculare"*: showing a solid "cell-nest" of undifferentiated epithelioid cells sharply demarcated from the surrounding stroma. (Figs. 557 and 558 by courtesy of W. F. Harvey, E. K. Dawson and J. M. R. Innes, Research Laboratory, Royal College of Physicians, Edinburgh.) × 150.

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[1] *ἄρρην, arrhēn*, a late Attic form of *ἄρσην, arsēn*, male—*cf.* arsenic: and *βλαστέω, blasteō*, a late form of *βλαστάνω, blastanō*, to make to grow, to produce. *See also* footnote on p. 297.

Oöphoroma folliculare or **Brenner's tumour** is generally a small benign growth found sometimes in the wall of pseudomucinous cystadenomas. It is supposed to arise from germinal epithelium, and the microscopical picture shows nests of epithelial cells in a fibro-cellular matrix. It has no disturbing influence on sexual characters.

The Dysgerminoma of G. Meyer occurs at a relatively early age. It gives rise to no endocrine disturbance, but in a large proportion of cases it has been associated with sexual deficiency—infantilism or pseudo-hermaphroditism. It takes its origin from undifferentiated germinal cells, and, in its histological appearance, it resembles a seminoma (Fig. 532, p. 908). The tumour is either benign or of low malignancy, and its removal is said to bring about development to maturity of the genitalia.

PAR-OÖPHORON

("Parovarium")

Cysts of the par-oöphoron may be small and unimportant, generally unilocular and filled with clear fluid. A very large cyst, the wall of which is thick and lined by columnar ciliated epithelium, is, however, not uncommon. It is situated usually between the layers of the broad ligament. The ovary is attached to the side of the cyst and the uterine tube stretched over it. It is of importance clinically chiefly because of the large size to which in some cases it may attain.

CHAPTER XXVII

DISEASES OF THE BREAST

Structure of the Breast. Before considering hyperplasia, hypertrophy and neoplasia of the breast, some knowledge of its normal structure at various stages of activity is important. The mammary gland of the female is composed of a number of irregularly-shaped lobes separated from one another by dense connective tissue containing a varying amount of fat. Each lobe is provided with an excretory duct lined by stratified squamous epithelium. This **lactiferous duct** runs towards and opens on the nipple. The lobes are subdivided by a loose and cellular connective tissue, into lobules composed of alveolar ducts and alveoli. The walls of the alveolar ducts and alveoli consist of a basement-membrane and a lining of low columnar epithelium. Between this epithelial lining and the basement-membrane, a second layer of more flattened myo-epithelial cells or " basket-cells " is present. These are especially prominent near the excretory ducts, into which the alveolar ducts open, and are thought to act as smooth-muscle cells, and to facilitate the movement of the milk into the ducts. It is claimed by some writers that, at puberty and in the resting stage of the breast, the only epithelial structures present in the lobules are the ducts and their branches. The growth of the lobule, by increase in the length and complexity of the group of ducts which compose it, continues from puberty until the mature breast is formed. There is evidence that at puberty active budding of the ducts and the formation of acini occur, this growth being under the influence of the ovary—the ripening of the ovarian (Graafian) follicles and the formation of the corpus luteum. For the *rôle* of the pituitary under the influence of œstrogenic substances, *see* p. 806 *et seq.* During pregnancy, the breast undergoes a true hypertrophy, more or less continuously progressive, until parturition. This hypertrophy consists of a glandular increase, with extension of the existing, and the formation of new, ducts and acini. It is associated with increased vascularity and a gradual replacement of the connective tissue and fat by these new formations. This proliferation is due to the action of the hormone of the corpus luteum of pregnancy and also to placental stimulation. When the placental stimulation is withdrawn as a result of delivery, proliferation ceases and secretion becomes active. The relative degree or extent of the transition from ducts to acini varies in different cases, and, in the actively-secreting breast, lobules which are not functioning as secreting-tissue during lactation are still present. When lactation ceases, the secreting-acini, which have been formed and differentiated during pregnancy, degenerate and gradually disappear. In many cases, the return to the " normal," *i.e.*, non-secreting, condition, is not complete and some hypertrophy of glands or some fibrosis of stroma remains—a point of importance the neglect of which may lead to erroneous diagnosis in biopsy-specimens.[1]

CONGENITAL MALFORMATIONS. Congenital absence of the nipple is extremely rare. **Absence** of one or of both breasts—**amastia**—occurs, but is always associated with other developmental defects. **Imperfect development** is sometimes seen in association with defects in the genital organs, such as absence or imperfect development of the ovaries. **Infantile hypertrophy** may be found—the mammary gland showing an abnormal degree of proliferation of its glandular elements. **Abnormal development**—" **gynæcomastia** "—is sometimes seen in the male breasts, especially about the age of puberty, and an imperfect secretion of milk occasionally takes place.

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[1] E. K. Dawson: " Sweat Gland Carcinoma of the Breast," *Edinburgh Medical Journal*, 1932, **39**, 409 : " Carcinoma in the Mammary Lobule and its Origin," *ibid.*, 1933, **40**, 57 : " Prognosis in Mammary Carcinoma in Relation to Grading and Treatment " (with M. C. Tod), *ibid.*, 1934, **41**, 61 : " A Histological Study of the Normal Mamma in relation to Tumour Growth," *ibid.*, 1934, **41**, 677, and other papers from which we have obtained much information on the structure of the breast and on tumours of the organ.

Supernumerary mammary glands—polymastia, in the Middle Ages thought to be the sign of a " witch "—are not uncommon, and may be situated a little below, and internal to, the normal glands, in the region of the anterior axillary fold, in the middle line over the sternum, on the abdomen, in the groin or upon the labia majora, and, much more rarely, on the back, shoulders, arms, or other parts. These glands may be normal in structure and function ; but, as a rule, they are merely rounded masses of mammary tissue without excretory ducts and without nipples. When represented only by **accessory nipples,** the condition is known as **polythelia.**

The influence of the internal secretions of certain of the ductless glands upon the mammary glands is discussed in the chapter dealing with the endocrine organs (p. 806 *et seq.*), and also in the previous chapter (p. 916 *et seq.*).

ATROPHY or **INVOLUTION** supervenes as a physiological process after the menopause. Sometimes the atrophy is not associated with diminution in the size of the breast—an overgrowth of adipose, and even of fibrous, tissue replacing the atrophied glandular structure. Owing to irregular ovulation during the period leading to the menopause, the atrophy may be interrupted by irregular periods of proliferation, and cystic development occur.

HYPERPLASIA and "HYPERTROPHY." The female breast undergoes periodic changes during sexual life as a result of ovarian activity. If that ovarian activity is abnormal or irregular, there may be interference with the normal cycle of proliferation and involution preceding and following menstruation. If the ovarian stimulation is in excess, undue hyperplasia or delayed involution may result. This hyperplasia—called " mazoplasia " by Cheatle and Cutler [1]—may be local or diffuse. The painful nodules which are sometimes found in the breasts of young girls at, immediately following, or sometimes before the establishment of puberty, and also in later life during menstrual periods, are due probably to this over-stimulation of the glandular tissue at localised or more diffuse areas. If the changes affect both the glandular and connective tissues, a condition of **fibro-adenosis** may be produced. Hyperplasia of the breast or mazoplasia (it should *not* be called " hypertrophy " or " mastitis "), is thus an exaggerated form of the changes which take place in the breast in infancy, at puberty, and during pregnancy and lactation, as well as at the menopause. Cheatle and Cutler (*loc. cit.* p. 92) regard that form of hyperplasia which is characterised by the **development of cysts—" cystiphorous desquamative epithelial hyperplasia "** (which often supervenes during the earlier part of the climacteric period, when ovarian function is becoming irregular) as a pathological process distinct from the foregoing. It should *not* be called " chronic cystic mastitis," and, though itself apparently not neoplastic in nature, neoplasia, both simple and malignant, may supervene in breasts which have been its seat (*cf.* pp. 290 and 937 *et seq.*). Similar conditions arise in ovarian and uterine diseases. An enlarged and apparently " hypertrophied " breast is often associated with general adiposity and may show comparatively little or no hyperplasia of the glandular tissue itself. In some cases, the enlargement is due to a considerable increase in the connective tissue.

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[1] " Tumours of the Breast," by G. Lenthal Cheatle and Max Cutler, Arnold & Co., London, 1931, p. 77 *et seq.*

DEGENERATIONS. Fatty and **myxomatous degenerations** in the secreting structures are not common. The latter sometimes supervenes in areas of "chronic fibroid mastitis" (fibro-adenosis) or in fibromas.

INFLAMMATION:—

(*a*) **Inflammation of the Nipple and Areola** is liable to occur at any period of lactation. The parts become conical, red, and swollen. Superficial ulceration, abrasions, and fissures, with a certain amount of sero-purulent exudate, are sometimes present. The inflammation may spread and cause abscess-formation in the substance of the breast, though more usually it is confined to the nipple and its areola.

(*b*) **A "Chronic Inflammatory"** condition of the nipple and areola was described by Paget, and was regarded by him as a precursor of carcinoma (pp. 940–2).

(*c*) **Acute Mastitis** rarely occurs except during the period of lactation; though it has been observed in infancy and childhood and in the course of infectious diseases, especially in mumps. Acute mastitis occurring during the period of lactation is due usually to infection from the nipple, the invading bacteria being commonly staphylococci or streptococci. The breast becomes swollen and hyperæmic, and the overlying skin reddened. The inflammatory reaction may be localised or widespread, and the process sometimes subsides without suppuration. Abscess-formation, however, is apt to occur—the suppuration being confined to localised areas, or infiltrating widely. The pus tends to burrow and may make its way into the ducts and be secreted with the milk, or may be discharged externally through the skin. The abscess is situated in the tissue beneath the areola: in the breast itself: or in the tissues subjacent to the breast—an abscess in the latter position being due, however, more usually

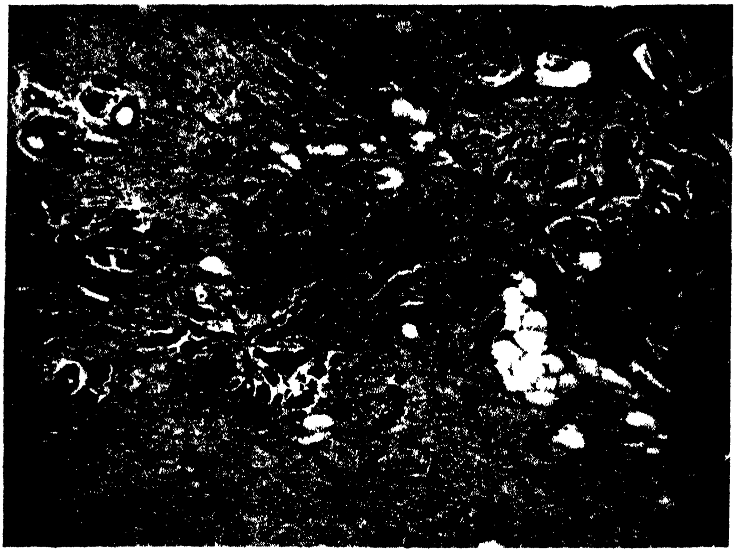

FIG. 559. *Fibro-Adenosis* ("*Chronic mastitis*") showing an area of glandular hyperplasia and extensive cellular proliferation. There was no evidence of malignancy. Hæmatoxylin and eosin. × 70.

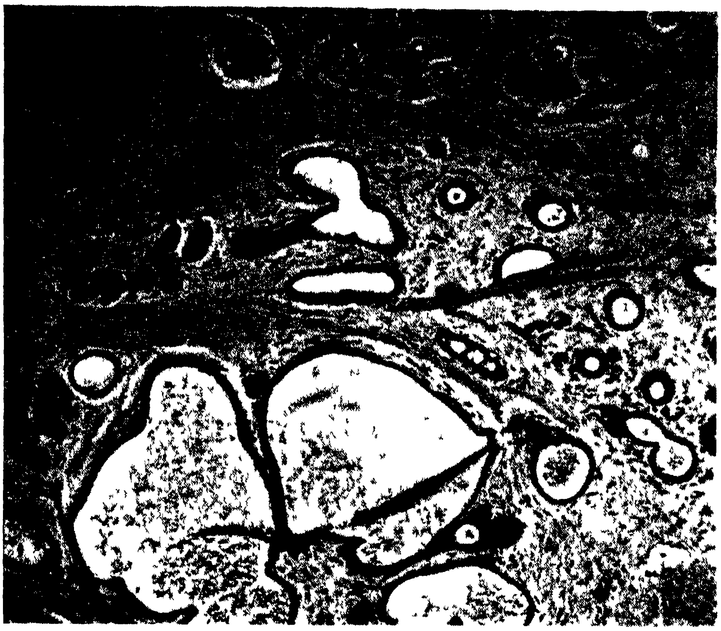

FIG. 560. *Fibro-Adenosis* ("*Chronic mastitis*") showing dilatation of ducts and acini with marked fibrosis of the interglandular tissue. Hæmatoxylin and eosin. × 70.

to necrosis or tuberculosis of a rib or of the sternum, though, in some cases, it is produced by an extension of suppuration from the deeper parts of the breast itself.

(*d*) **Fibro-Adenosis** (or so-called "Chronic Mastitis"). Most of the conditions loosely and often erroneously described as "chronic mastitis" are

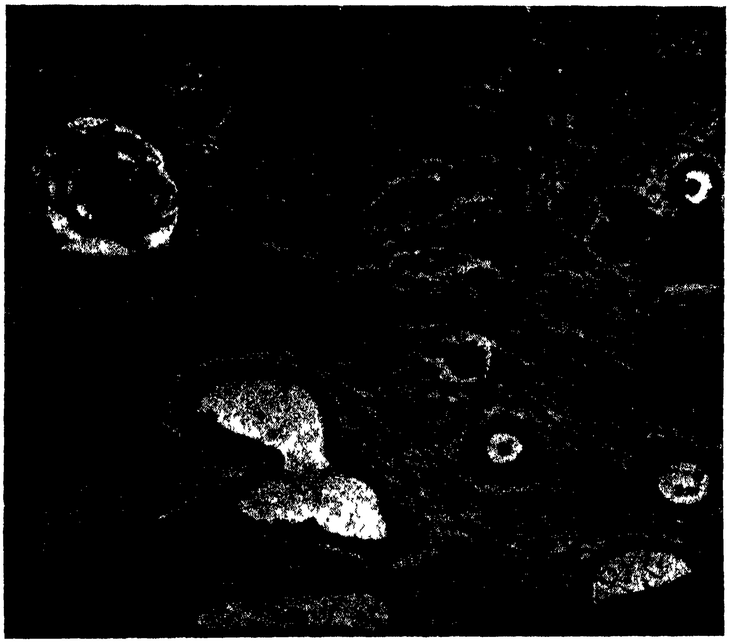

FIG. 561. *Fibro-Adenosis* ("*Chronic mastitis*") showing periphery of area in Fig. 560. Hæmatoxylin and eosin. × 120.

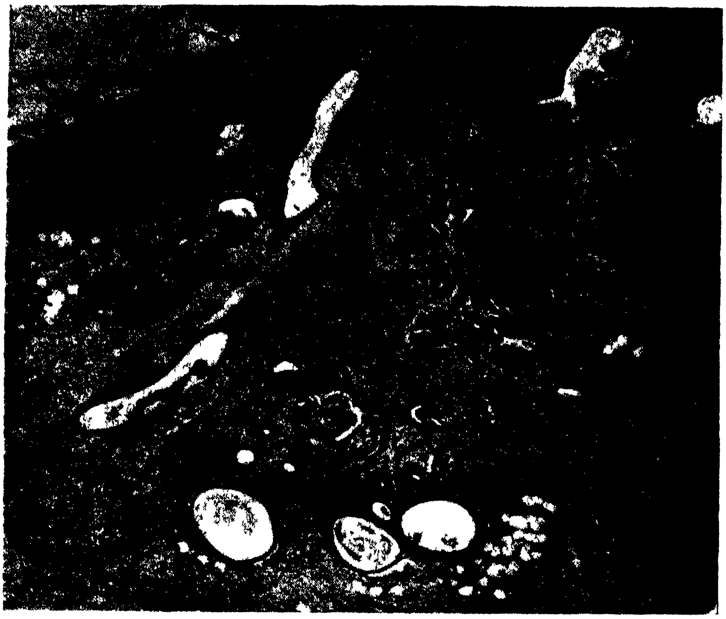

FIG. 562. *Fibro Adenosis* ("*Chronic mastitis*") showing localised area of both glandular and inter-acinous fibrous-tissue hyperplasia Hæmatoxylin and eosin. × 25.

proliferative and degenerative in character rather than inflammatory. There seems little doubt that they are due to abnormal or excessive stimulation of the breast-tissues by ovarian hormones. Hyperplasia of the glandular tissue or a hyperplasia of the interacinous tissue is present. The lesions may be diffuse : or localised to several lobular areas : or even to a small part of the

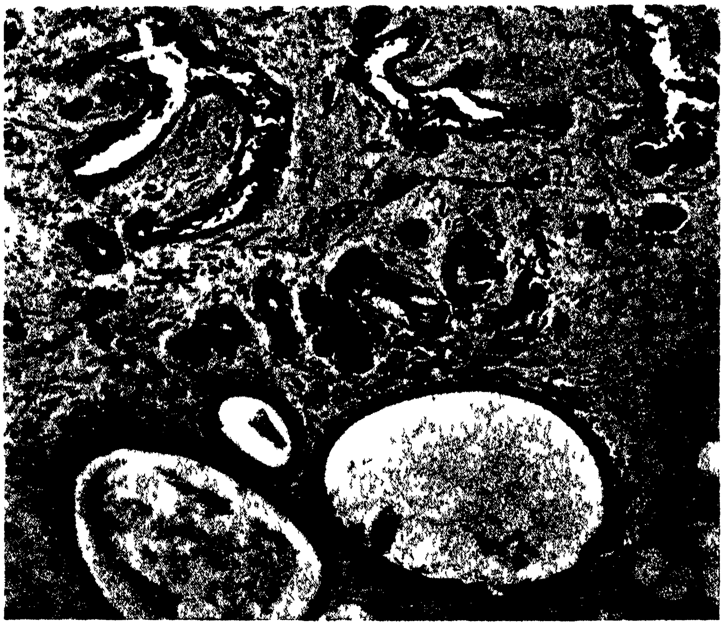

FIG. 563. *Fibro-Adenosis* ("*Chronic mastitis*"): higher-power view of the same, showing formation of dilatation-cysts, slight epithelial proliferation in one of these, and degenerated contents. Hæmatoxylin and eosin. × 95.

whole gland. In those cases in which the proliferative changes are confined mainly to the glandular elements, the adipose tissue is scanty and the glandular tissue abundant, diffuse in its distribution and tough in consistence. In some varieties (p. 935), cyst-formation is common and the ducts are often dilated : papillomatous epithelial ingrowths into the acini and into the cystic dilatations are often a prominent feature : and these cellular proliferations may completely fill the ducts. The cysts, which may contain mucus-like material and sometimes cholesterol-crystals, and the giant-cell tissue associated with cholesterol-deposits, are the result of degenerative changes in the acini or ducts. The type in which the cysts are numerous and the epithelial hyperplasia abundant has been called "**Schimmelbusch's disease,**" and is regarded by Cheatle and Cutler as the only form which is pre-cancerous—three stages being distinguished by them[1]: **desquamative epithelial hyperplasia,** which causes the cysts : definite but at first **benign neoplasia,** with formation of papillomata : and, accounting for some 20 per cent. of all cases of carcinoma of the breast, this " cystiphorous " form ends in the development of **malignancy.** According to Sampson Handley " chronic mastitis " and " chronic cystic mastitis " are stages in the same process which commences as a persistent lymph-stasis, is slow in its course, and not infrequently ends in carcinoma. Ewing, in his book on " Neoplastic Diseases "[2] (1940), observes that : " In chronic mastitis single small cancer nodules may appear, and I believe their preliminary stages may be traced in other portions of the breast, chiefly in the ducts. Here one finds hyperplasia of lining cells. . . . Yet other cells show more active proliferation, increase in size and in nuclear chromatin . . . and it is possible to trace such cells into types closely approaching those seen in early carcinoma." Similarly, Robert Muir, in his " Text-Book of Pathology "[3] (1936), writes : " We believe that in the large majority of cases it (carcinoma of the breast) is preceded by the hyperplastic changes in the ducts and acini . . . , the extreme of which is intraduct carcinoma." Other authors, however, maintain that " chronic proliferative mastitis "—so-called —is never a precursor of carcinoma, and take the view that " chronic mastitis " and carcinoma may each be the independent sequel of some chronic irritative process, and that *both* lesions may thus be present in the same breast as coincidences. It is, of course, a difficult matter to prove that both conditions are of necessity the associated stages of one single progressive pathological process, but we quote the foregoing considered opinions of these well-known authorities in favour of this generally-held view. It is only fair, however, to state that the authors of this textbook are not themselves in entire agreement with each other in regard to this difficult problem, and it must be admitted that there is the possibility that carcinoma may arise from the glandular epithelium independently and might thus tend to be localised in and around the areas in which that epithelium is already hyperplastic, whether the preceding hyperplasia or " adenosis " had been brought about by a " chronic inflammatory " process : or, as is more likely, through the influence of hormones (or the absence of certain of these) : or by a combination of both of these agencies. Much of the confusion which has arisen with regard to the problem has originated from the somewhat loose employment of the term " mastitis " to denote, not only chronic irritative inflammatory processes on the one hand, but also the non-inflammatory changes brought about by hormones (or a deficiency of these) on the other, or by certain still unknown factors at work in the production of malignant disease.

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[1] *Loc. cit.*, p. 92.

[2] " Neoplastic Diseases, a Treatise on Tumours," by James Ewing, Cornell University, 4th edition, 1940, p. 19.

[3] " Text-Book of Pathology," by Sir Robert Muir, Glasgow, 4th edition, 1936, p. 916.

The interacinous connective-tissue hyperplasia may be cellular (Fig. 561) or densely fibrous (Fig. 562); the amount varies in different cases, and there may be wide separation of the ducts and acini, with varying degrees of atrophy. Infiltration with small round cells (lymphocytes and plasma-cells) is often a prominent feature.

The various forms of hyperplasia of the breast, especially those which remain localised, may—on account of the induration, the retraction of the nipple, and the period of life at which they usually occur—closely simulate scirrhous cancer clinically; and, where proliferative changes in the epithelium are a pronounced feature, the microscopical characters may come to resemble more or less closely those of a fibro-adenoma or of a scirrhous cancer. In the same breast, it is comparatively common to find " chronic proliferative mastitis " or fibro-adenosis in association with scirrhous cancer, but the causal relationship between the two is, as we have just indicated, a difficult matter to prove.

CYSTS. Galactoceles, or **" milk-cysts,"** may occur during pregnancy, but are commonest during lactation. They are simply retention-cysts, and are due to narrowing or obliteration of ducts or gland-acini by inflammatory reactions or blocking by retained and inspissated secretion. The inflammatory changes may be so pronounced that, on clinical examination, the cyst may be mistaken for a solid tumour. Multiple cysts, varying in size but usually small, are not infrequently found in cases of " chronic mastitis " and are due to distension of remnants of the glandular tissue during the retrogressive changes in the organ at, or subsequent to, the menopause. **Parasitic cysts** such as hydatids are rare.

TUBERCULOSIS, SYPHILIS and **ACTINOMYCOSIS** of the **BREAST** are referred to in Chapter III, pp. 76, 81, and 92 respectively.

TUMOURS OF THE BREAST

These may, for descriptive purposes, be classified into those of the nipple and areola, and those of the body of the organ or corpus mammæ. (*See also* Chapter XIII, on Special Varieties of Neoplasm, *passim*, *e.g.*, pp. 341–50, Figs. 178, 181–5, and 187–9.)

A. OF THE NIPPLE AND AREOLA :—

Melanomas, myxomas, angiomas, and **papillomas** are rare. **Epitheliomas** —especially the form known as **Paget's disease of the nipple**—call for a more detailed description.

Paget's Disease of the Nipple. This somewhat rare disease, said to form about 1 per cent. of all breast-cancers, was described first by Sir James Paget, in 1874, as a disease of the nipple and mammary areola in some ways resembling chronic eczema, and " followed " almost invariably by cancer of the mammary gland itself. In the majority of his cases—to quote Paget's own words[1] —the patch "had the appearance of a florid, intensely red, raw surface, very finely granular, as if nearly the whole thickness of the epidermis were removed; like the surface of a very acute diffuse eczema, or like that of an acute balanitis. From such a surface, on the whole or greater part of the nipple and areola, there was always copious, clear, yellowish viscid exudation. The sensations were commonly tingling, itching, and burning, but the malady was never attended by disturbance of the general health. I have not seen this form of eruption extend beyond the areola, and only once have seen it pass into a deeper ulceration of the skin, after the manner of a rodent ulcer.

"In some of the cases, the eruption has presented the characters of an ordinary chronic eczema, with minute vesications, succeeded by soft, moist, yellowish scabs or scales, and constant viscid exudation. In some it has been like psoriasis, dry, with a few white scales, slowly desquamating; and in both these forms, especially in the psoriasis, I have seen the eruption spreading far beyond the areola in widening circles, or, with scattered blotches of redness, covering nearly the whole breast."

Many authors now regard the condition as carcinomatous from the outset, and commencing as a glandular carcinoma of the large ducts of the nipple with, at a later period, a slow invasion of the stroma and the production of a scirrhous type of carcinoma. This invasion, by permeation or secondary fibrosis of the subareolar lymphatic plexus, interferes with the normal lymph-drainage of the nipple, and may lead to the production of a viscid, clear-yellowish, or slightly-turbid, discharge.

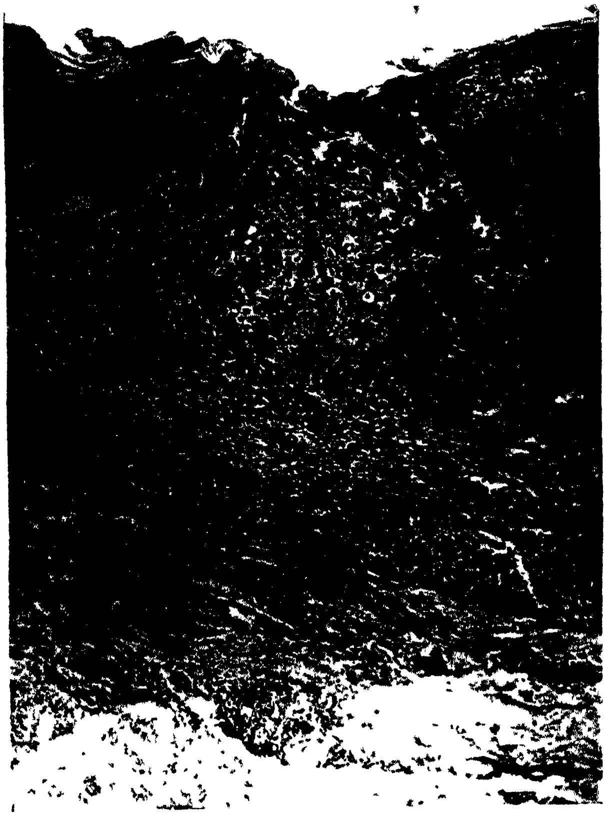

FIG. 564. *Paget's Disease of the Nipple. See* text. ×60.

The nipple becomes indurated and retracted; and, later, as the process advances, it is destroyed. In the subjacent breast-tissue, there can generally be felt a hard mass of new growth, commonly a slow-growing cancer of scirrhous type, palpable usually in from one to two years or more after the appearance of the disease in the nipple. For this reason some authorities believe that it is an infective process in the nipple, which produces a chronic eczema, which in turn predisposes and leads up to the cancerous condition of the breast. It is probable, however, that the disease is malignant from the first, and is a slow-growing carcinoma, commencing in the lactiferous ducts near their outlet, and gradually spreading to involve the surface, and also the deeper structures.

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[1] Sir James Paget, "On Disease of the Mammary Areola preceding Cancer of the Mammary Gland," *St. Bart.'s Hosp. Reports*, 1874, **10**, 87. Keith Inglis, "Paget's Disease of the Nipple," Oxford Univ. Press, London, 1936.

On microscopical examination, a vertical section through the affected areola shows areas of epithelial proliferation ; and, especially in the deeper layers of the epidermis, the presence of large, pale, rounded, or ovoid cells, with faintly staining cytoplasm, and large, deeply-stained nucleus, usually single, but sometimes multiple—the so-called "Paget-cells" (Fig. 564). In the nipple, there is a similar lesion, and also irregular proliferation of the cells lining one or more of the ducts, a condition which can be traced inwards and found to be continuous with the subjacent mammary tumour, which is usually of ordinary scirrhous type. Robert Muir believes that the tumour starts as a carcinoma in the ducts, along which it spreads, penetrating between the cells of the epidermis, and that it is not produced by proliferation of the cells of the epidermis. Enlargement and malignant infiltration of the lymph-nodes in the axilla complete the picture of a scirrhous tumour.

B. OF THE BREAST OR CORPUS MAMMAE:—

Tumour-formation in the body of the breast is rare between birth and puberty, and during that period the development of malignancy is practically unknown. The stimulus of bodily growth at puberty and in subsequent years seems to create favourable conditions for neoplasia, but the tumours which develop between the ages of thirteen and twenty are fibro-adenomatous in type and sometimes encapsuled. Many of these must be regarded as exaggerations of physiological growth, characteristic of the stage of mammary development, and due to over-activity of the ovarian hormones. This hyperplasia of normal breast-tissue may be localised to single lobules, and sometimes, about the age of puberty, as described on p. 935, gives rise to painful swellings simulating tumours. Histological examination shows that the new tissue is comparable with the normal developing mamma at that age.

> E. K. Dawson [1] writes : "It is difficult to understand why such glandular tissue-increase should not occasionally pass from adenosis through adenoma to malignant growth, but apparently this does not happen. . . . I have not yet found described and illustrated any case of malignant [mammary] epithelial growth which convinces me regarding its origin as an adenoma or a fibro-adenoma, nor does any of the large number of these benign tumours examined by me suggest the likelihood of such epithelial malignant transformation."

Whilst this view is deserving of full consideration, it is by no means universally accepted. It is *not* in accord with the observations of such authorities as James Ewing and Robert Muir (*see* p. 939) ; nor are the authors of this textbook in full agreement with one another as to which of these opinions has the greater amount of evidence in its support, in which connection *see* p. 347.

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[1] "A Histological Study of the Normal Mamma in relation to Tumour Growth," by E. K. Dawson, Royal College of Physicians Laboratory, Edinburgh, *Edinburgh Medical Journal*, 1934, **41**, 677.

During the period of pregnancy and lactation, malignant growths may appear to develop rapidly, and some of these arise from simple (non-malignant) tumours, but the evidence seems to point strongly to the fact that such growths originate from the epithelium covering papilliform intra-cystic villi in these tumours or from the lining-cells of the ducts, and that the proliferative changes in the epithelium were present before the pregnancy, and became manifest as the result of the stimulation to growth and the vascularity associated with this active reproductive period. These changes in the breast appear to be exaggerated as a result of the increase in pituitary activity produced by the action of the œstrogens (p. 916).

Based on an examination of the literature and wide histological experience, E. K. Dawson states:

FIG. 565. *Simple fibro-adenoma (or fibro-cystadenoma) of Breast.* × 50.

> "It seems therefore justifiable to assume that adenosis [glandular increase or overgrowth] is an essentially physiological response to growth-stimuli which affect mammary tissue, and though the new tissue produced may be excessive in amount, exaggerated in type and unequal in distribution, . . . at no stage has any association with malignant epithelial development been traced." [1]

(But for contrary views in this connection see general chapter on Tumours, pp. 344–7.)

Simple Tumours. Fibromas, lipomas, myxomas, pure chondromas, mixed cartilaginous tumours, and angiomas have been described, but are rare. Tumours in which the glandular elements alone have proliferated—adenomas—are uncommon, and usually become apparent during pregnancy and lactation. Probably they are previously undetected tumours which have taken on more rapid growth during the active stage of development of the glandular tissue.

Fibro-adenomas (Fig. 565), on the other hand, are common. Great variations are found in the relative amounts of the fibrous and glandular elements in such tumours, and also in their characters. Soft and hard varieties occur, the connective tissue in the former being abundant, highly cellular, and perhaps also myxomatous ; whilst, in the harder varieties, it is scanty and more fibrous. Hard fibro-adenomas are, as a rule, small and slow-growing ; whilst the softer varieties may be larger and—though usually also of comparatively slow growth—may sometimes grow more rapidly, especially on the occurrence of pregnancy.

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[1] *Loc. cit.*, p. 677.

In the soft variety—the **intra-canalicular**[1] **fibro-adenoma** (Fig. 158, p. 325) —the fibro-cellular tissue-proliferation predominates, and this proliferated tissue, which Cheatle states commences internal to the elastica of the ducts, forms polypoidal masses projecting into the lumen and is covered by the epithelial lining. The epithelial growth keeps pace with the fibro-cellular proliferation. As a result of this fibro-cellular invagination and growth, the walls of the ducts may be so approximated that, on microscopical examination, the tumour presents the appearance of a soft fibroma with curved and branching narrow clefts lined with epithelium (Fig. 158, p. 325). The hard variety—the **peri-canalicular**[1] **fibro-adenoma**—is composed of glandular tissue, which is really proliferated normal breast-tissue, and an overgrowth of connective tissue, the new fibrous tissue surrounding the ducts. These tumours are encapsulated, and do not infiltrate the surrounding tissues. On naked-eye section, the surface is dull white, or perhaps slightly pinkish in tint; and the cut surface usually bulges —a point of some importance in contra-distinction to the retracted concave appearance of the cut surface often seen in scirrhous cancers of the breast. It is often difficult, and sometimes well-nigh impossible, to differentiate certain examples of fibro-adenomas from "chronic mastitis" with overgrowth of connective tissue and irritative proliferation of the enclosed epithelial spaces and ducts; and it is probable that many cases diagnosed as "fibro-adenoma" are in reality due to such chronic proliferative changes and would be better termed "**fibro-adenosis**" (p. 937 *et seq.*). Cystic spaces may be developed in a fibro-adenoma, the resulting tumour being known as a cystic adenoma or **cystadenoma** of the breast. If the epithelium lining these cystic spaces grows more rapidly than the supporting connective-tissue wall, papillary ingrowths are produced (Fig. 566). These are often highly complex or branching in structure, giving rise to a foliaceous appearance of the tumour on naked-eye section. Such tumours, in some instances, attain a very large size, and are known as papilliferous cysts. Extensive hæmorrhage may occur into their interior; their stroma is often mucinoid; and they may undergo necrotic and ulcerative changes. Microscopical sections from cystic breasts may show two types of epithelial cells—those staining deeply with hæmatin and eosin, and those which are paler or "pink" in colour. The latter are probably degenerative or inactive forms of the former, and tumours arising from the pale cells have sometimes been described as sweat-gland tumours. In view, however, of the observations of E. K. Dawson [1] that this "pale" epithelium is *not* present in the normal breast, and that it is found only in, or associated with, cysts in which the epithelium, during its proliferation, has undergone degenerative changes, it is difficult to accept the view of Ewing [2] that tumours which he observed and which were characterised by the presence in them of a "pale epithelium" which stains red or "pink," are really sweat-gland carcinomas of the breast. It seems more likely that such tumours originate in the "pale epithelium" of cystic spaces.

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[1] These terms "peri-" and "intra-canalicular" are in common use, but their meaning is by no means self-evident. When applied to a tumour of the breast, they suggest that it has grown around or in some special "canal." In explaining the mechanism by which these two varieties of tumour arise, Cheatle and Cutler (*loc. cit.*, pp. 170 and 457) call attention to the *rôle* of the **elastic tissue** in the breast, and the importance and necessity of differentially staining it for the study and elucidation of the origin of these tumours. Only the **ducts** (except their smallest terminal twigs, which, like the gland-acini, do *not*, as a rule, possess an "elastica") **have this definite layer** of **elastic tissue,** immediately external to the comparatively thin layer of subepithelial connective tissue which forms the basement-membrane upon which the epithelial cells of the ducts stand. Thus, in the case of the ducts, if hyperplasia or neoplasia of this subepithelial connective tissue takes place, the overgrowth, confined within the elastica, will extend in the direction of least resistance, *i.e.*, inwards towards the lumen of the tubes. The walls of these tubes are thus pressed upon and invaginated into their own lumen by what in section show as irregularly-rounded masses of proliferating connective tissue, each carrying in and being itself surrounded by a layer of the epithelium, and the result is an "**intra-canalicular**" **fibroma** or "**fibro-adenoma**" like that illustrated in Fig. 158, on p. 325. If, on the other hand, the fibrous proliferation takes place around the **acini** (and the immediately-adjacent minute ducts originating from these), which do *not* possess this limiting and confining elastic layer, or if the growth originates from the **general interstitial connective tissue of the breast external to the elastica of the larger ducts,** the result will be **peri-canalicular,** as illustrated in the series of Figs. 559–63.

Duct-Papilloma. This is an adeno-papillomatous ingrowth—often highly complex in structure—which develops and projects from the walls of one of the milk-sinuses or larger ducts near the nipple. Such tumours may also arise from the smaller ducts and may have a diffuse distribution, forming a "**papillomatosis.**" The affected channel becomes correspondingly dilated, the contained mass of tumour being usually extremely vascular, and dark-red in colour, and frequently giving rise to hæmorrhage, with blood-stained fluid exuding from the nipple on squeezing.

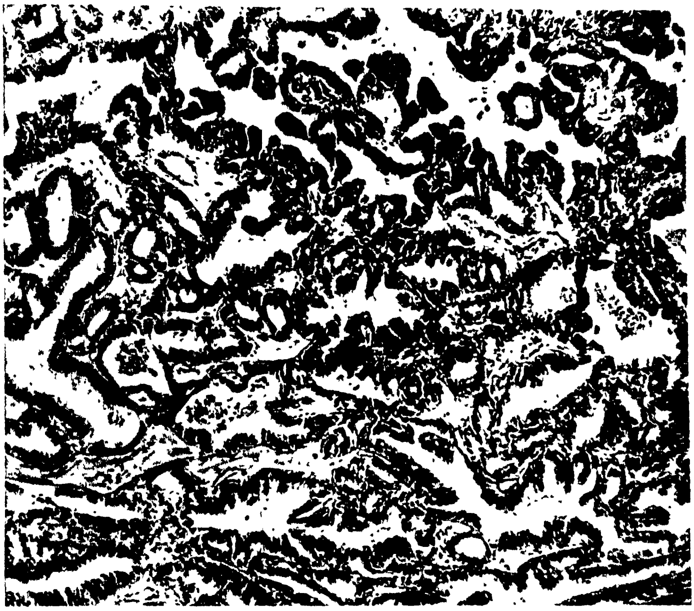

FIG. 566. *Complex Adenoma (papillary cystadenoma) of Breast.* The acini are dilated and show numerous papilliform ingrowths or infoldings. × 50.

Malignant Tumours. Sarcoma is much rarer than carcinoma, constituting less than some 3 to 5 per cent. of breast-tumours, and is of the spindle- or round-celled—less commonly of mixed-celled—type. These types of tumour do not call for further description, as, with regard to their appearance, methods of spread, etc., they resemble similar tumours in other situations (p. 316 *et seq.*). Mucinoid (myxomatous) degeneration, as well as necrosis and hæmorrhage, may supervene in them.

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[1] "Sweat Gland Carcinoma of the Breast," by E. K. Dawson, R. C. P. Laboratory, Edinburgh, *Edin. Med. Jour.*, 1932, **39**, 409.

[2] "Neoplastic Diseases," by James Ewing, 4th edition, 1940, p. 576.

Melanomas of the breast, now regarded as epithelial or carcinomatous, rather than sarcomatous (pp. 323–4), are secondary to tumours arising in the nipple, pigmented tissue of the areola, or from pigmented tissue elsewhere in the body.

Carcinoma is the commonest and most important neoplasm of the mammary gland. Its relative frequency is variously estimated as about 50 to 80 per cent. of all breast-tumours. With regard to its sex-incidence, it is rare in the male breast; and in women, those between the ages of fifty and fifty-five are most liable to the disease. The main pathological varieties of such tumours are the **scirrhous, encephaloid** or **medullary,** and **colloid** types; whilst, in a certain proportion of cases, a glandular type of structure and arrangement in acinous spaces is maintained, the type of tumour being then known as adenocarcinoma. All intermediate forms between these main " types " occur; and it is not uncommon to find different portions of an individual tumour exhibiting two or more—and even all—of these variations of structure. Tumours, which are typically scirrhous in their central or older portions, may be softer and more actively growing at their periphery, *i.e.*, more encephaloid (or medullary) in type and *vice versâ*. Imperfect acinous spaces are of common occurrence in certain parts of scirrhous and encephaloid growths; whilst

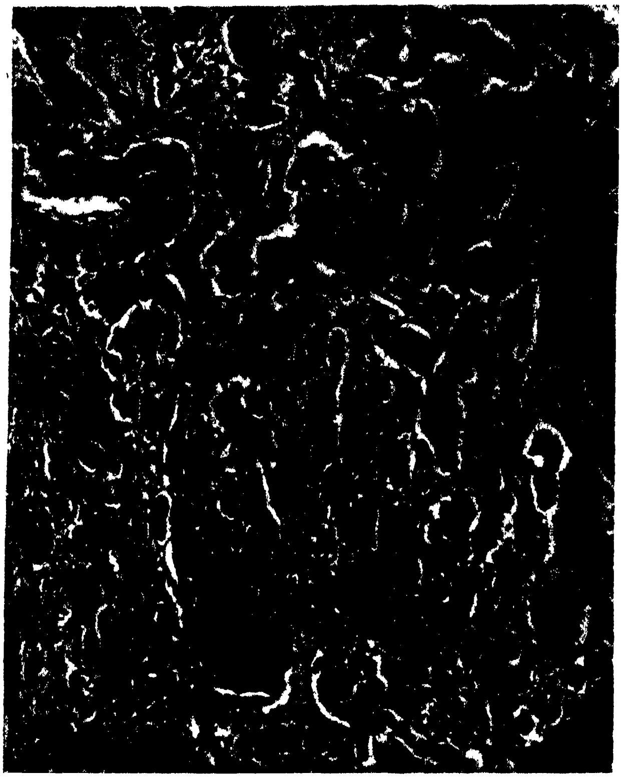

FIG. 567. *Scirrhous Cancer of the Breast*, showing groups of cancer-cells of various sizes in dense fibrous tissue. Hæmatoxylin and eosin. × 90.

mucinoid (" colloid ") degeneration, though comparatively rare, may supervene in any variety of carcinoma (Fig. 189, p. 349). Histological descriptions of these tumours will be found in the Chapter on Tumours (pp. 340 *et seq.* and Figs. 178 to 189 on pp. 344 to 349); and reference need be made here only to certain facts more particularly applicable to such tumours when occurring in the breast.

Spheroidal-celled Scirrhous Carcinoma or Scirrhus. The commonest malignant tumour of the breast is the **scirrhous** or hard variety of carcinoma (spheroidal-celled cancer) (Figs. 178 and 181–5 on pp. 344–6: and Figs. 567–8). The ordinary nodular scirrhous tumour is a comparatively slow-growing neoplasm which may appear in any part of the organ, but most frequently in the upper and outer quadrant. It is dense, and, when palpated against the ribs, exhibits a " wooden," or almost " stony," hardness. The knife passes through it with a grating or creaking sensation, and the central, *i.e.*, the oldest and densest, part of the cut surface, becomes slightly concave, owing to the dragging of the contracted cicatrix-like fibrous tissue, which has a dull whitish appearance. The spreading margin has a slightly more translucent, pearly-white or, sometimes, greyish-pink appearance, and may show little red points of hæmorrhage. Such growths may *appear* to be "circumscribed," or " nodular," or they may be " diffuse " ; but, in either case, they do not show any encapsulation, but spread irregularly into the surrounding tissue. The nipple, if the tumour be situated at or near it, tends to be drawn up to a higher level than its fellow of the opposite side, and to be retracted or drawn backwards into the breast (Fig. 178, p. 344). As the tumour spreads, it infiltrates the remaining breast-tissue and the surrounding structures and invades the tissue-spaces and lymph-channels. The superficial layers of the pectoralis major and other subjacent structures are, in time, likewise involved ; and the infiltration may continue through the pectoralis major, and come to involve the intercostals, ribs, pleura, anterior mediastinum, and lung. There may also be direct lymphatic spread to the liver. The overlying skin becomes invaded in the later or, in some instances, in comparatively early, stages of the disease, with the production of, at first, adhesion, then dimpling and puckering, of the integument. The invaded area of skin may ultimately be destroyed by ulceration. At the same time, the cancer-cells spread, both continuously (by permeation) and also discontinuously (*i.e.*, by a process of malignant embolism), along the lymphatic

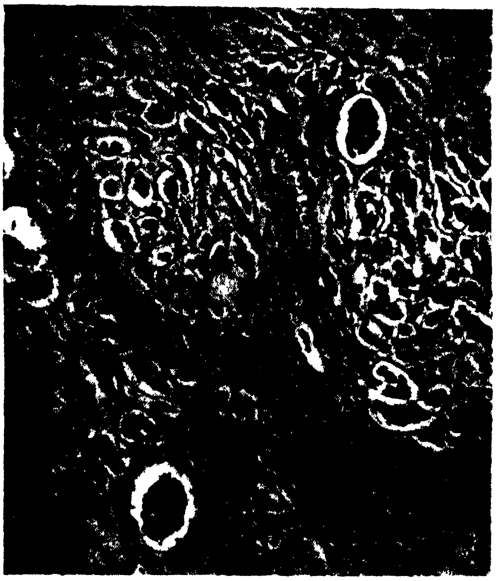

FIG. 568. *Scirrhous cancer of the breast* showing infiltration with masses of cancer-cells. Hæmatoxylin and eosin. × 70

channels which drain the breast-region. The majority of these lymphatics run outwards and upwards, opening into the pectoral group of lymph-nodes lying along the axillary artery toward the anterior part of the inner wall of the axilla. Some of the efferent lymphatics from the breast also pierce the sternal portion of the pectoralis major muscle, along with branches of the internal mammary artery, and of the pectoral and lateral thoracic branches of the axillary artery, and open into small lymph-nodes lying in the fascia on the deep aspect of the pectoralis major ; whilst a few also open into the chain of sternal lymph-nodes lying, within the chest-wall, along the course of the internal mammary. The infraclavicular and other lymph-nodes along the course of the superior thoracic artery may also be invaded. Sampson Handley, from the investigation of post-mortem material collated with clinical experience, emphasises the wide centrifugal spread of breast-cancer in the deep fascial lymphatic plexus, and, when sections were examined microscopically, observed its growing edge at points far removed from the breast, for example in the deltoid region or upper abdominal wall. The disease spreads from the affected axillary lymph-nodes to those higher up in the axilla, and to the subclavian and supraclavicular lymph-nodes, etc. ; and complications due to pressure upon, and involvement of, the axillary vessels and nerves may supervene. Permeation of the lymphatics related to the first, second and third intercostal arteries, and of the anterior mediastinal lymph-nodes, sometimes follows. Metastasis may also—usually comparatively late in the disease—take place by the blood-vessels, and secondary growths occur in internal organs and elsewhere. Metastases in the bones, especially of the vertebral bodies, pelvis, femur, humerus, ribs, and cranium, are comparatively common. In a high percentage of their post-mortems upon cases of carcinoma of the breast, the authors have found, in the bodies of the thoracic and lumbar vertebræ, such metastatic growths, which sometimes simulate the clinical picture of multiple myelomas. This extension is possibly accounted for by permeation through the lymphatics accompanying the intercostal vessels backwards towards the spine ; but, from recent work by Professor Oscar V. Batson in America,[1] it is not improbable that this spread to the bones of the vertebral column, skull and pelvis, in some instances takes place by a retrograde embolic metastasis by way of the veins (*see* p. 171). Secondary growths in the brain occasionally occur (p. 1150 and Fig. 736, p. 1147). Invasion of the other breast may take place by way of the inter-communicating lymphatics.

Certain forms of scirrhous tumour of the breast are exceptionally slow-growing and chronic. These **atrophic scirrhous** tumours are usually small, extremely hard, and fibrous, but are sometimes diffuse, the whole breast being infiltrated and shrunken, and the nipple retracted and drawn upwards. Occasionally, the skin, not only of the breast itself, but of a wide surrounding area, may be diffusely infiltrated—the so-called cancer "en cuirasse." On microscopical examination, the tumour-cells are scanty and degenerated, and are seen usually as small, compressed, elongated clusters, embedded in dense fibrous tissue.

Spheroidal-celled Encephaloid Carcinoma, Medullary or Soft Cancer (*cf.* p. 347). These are rapidly-growing tumours, to which, on account of their soft consistence, the above names have been applied. Other malignant tumours of the breast (*e.g.*, sarcomas and adeno-carcinomas), however, resemble them so closely in naked-eye appearance that some writers object to these terms, and prefer to call them "**Acute Cancers.**" They are highly cellular, the cells being irregular in size, and arranged in large solid clumps or masses embedded in a scanty connective-tissue stroma. They may form large, soft, bulging, more or less circumscribed, masses, the so-called "**tuberous**" form; or they may be diffuse tumours, rapidly infiltrating the breast and surrounding tissues—"**acute diffuse cancer.**" In both these varieties, the axillary lymph-nodes are involved early, and metastases in other organs rapidly supervene.

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[1] *See* footnote on p. 171.

Mucinoid ("**Colloid**") **Cancer** is a slow-growing and less malignant tumour, constituting from 1 to 2 per cent. of breast-cancers. Its characters are described in the Chapter on Tumours (p. 349).

Duct- or Intraduct-carcinomas are slow-growing, malignant tumours, consisting of tubular spaces lined by a single layer of columnar epithelium, or by several epithelial layers, that lining the lumen being columnar or cubical. In some instances, these spaces become dilated to form cysts, perhaps with papillary ingrowths; and, sometimes, the lumen may be almost filled with masses of rounded or irregular cells. The tumours are carcinomas, growing from the epithelium of the ducts, without necessarily breaking through their walls. The condition is not uncommon, is found at a relatively early age, and may be localised or may occupy a considerable portion of the breast. If the tumour invades the wall of the duct, it may infiltrate widely in the breast-tissue. On microscopical examination, the cells are rounded or irregular in shape and have a vesicular and often hyperchromatic nucleus.

Other tumours, which, from their association with the ducts of the organ, are sometimes included as "duct-cancers," have already been described, *e.g.*, the carcinoma developing in Paget's disease of the nipple (p. 940), which, as the disease progresses, develops the characters of a scirrhous cancer; and the adeno-papillomatous ingrowths projecting into the lactiferous ducts and cystic dilatations formed from these. The adeno-papilloma is probably a simple tumour, and therefore need not be further discussed here.

Trauma and Cancer of the Breast. Though a history of injury is often obtained from patients with cancer of the breast, the evidence of a causal relationship is in most cases doubtful. The examination of the breast after an injury may have merely called attention to the presence of a pre-existing but hitherto unsuspected early malignant growth. Sampson Handley,[1] however, records a few instances in which cancer appears to have followed an injury in patients in whom immediate examination of the breast had failed to reveal any evidence of new growth. Such patients he considers to have been predisposed to the disease, and the injury can, therefore, reasonably be regarded as having a causal relationship to the subsequent development of the growth. In the production of dissemination and metastasis, however, and apart from the question of actual causation, injury does appear to have considerable influence. The blow can act by setting free cancer-cells which have been lying quiescent in connective-tissue spaces or are only slowly permeating the tissues by lymphatic spread. Such cells may thus get into the blood-stream, and be carried to distant parts. It is important, therefore, as Sampson Handley points out, that "strenuous occupations and violent exertions should be forbidden, at any rate for some years, to a patient who has undergone an operation for breast cancer."

[1] "Trauma and Breast Cancer," by Sampson Handley, London, *Medical Press and Circular*, 1940, **204**, 436.

CHAPTER XXVIII

DISEASES OF THE NERVOUS SYSTEM

Preliminary Note. The writer of this chapter perhaps owes some apology to his readers for making it in parts rather fuller than is usual in a textbook of general pathology. He has tried to approach the subject, not from the "examination point-of-view," but from that of interest in a difficult and complex subject ; and he asks more particularly his student-reader not to attempt to overburden his memory with endless "neurological technicalities," but rather to make it his aim to master the general principles of pathology and apply them to the interpretation of what occurs in disease of an individual organ or tissue, of which he has already studied the normal anatomy and physiology. The writer has also illustrated this chapter somewhat profusely. Much of his original neurological material, including his collection of microscopical sections and photographic negatives, has been damaged or destroyed "by enemy action," when the West End Hospital for Nervous Diseases was wrecked on October 16th, 1940—thus rendering impracticable the future preparation by him of any more comprehensive work on cerebral tumours or general neuropathology, which he had hoped to write. He has therefore utilised here such of the photographic prints of these negatives as he had already prepared for this purpose and which he happened to have in his own home. He apologises for introducing this personal note here, but it also explains why in certain sections of the chapter subjects which would otherwise have been included have had to be omitted, whilst in others the illustrations are more numerous.

The writer (W. E. C. D.) wishes here gratefully to acknowledge personal grants from the Medical Research Council, which (together with help received from Mrs. Hugh F. Paul and her friends) made it possible to carry on at the West End Hospital for Nervous Diseases the research and photographic work which have been extensively utilised in this section of our textbook (*see* Preface, p. vii, and p. 1059).

In previous editions, this chapter was subdivided into separate sections dealing respectively with diseases of the membranes, the brain, spinal cord, peripheral nerves and ganglia. Although still adhering in the main to this arrangement, it has been found convenient to group together descriptions of the effects of certain diseases which may attack several or perhaps all of these component parts of the nervous system simultaneously, cross-references being given where necessary.

For fuller accounts of certain rare conditions with which we do not deal, we refer our readers to recent books on Neuropathology,[1] and, for detailed descriptions of the embryology, anatomy,[2] histology and physiology of the nervous system, to textbooks on these subjects.

Before proceeding to describe the diseases of the nervous system, it is, however, convenient to refer by way of introduction to a few of the more important anatomical and physiological points which have a special bearing upon the aspects of the subject which concern us here.

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[1] For example, "Pathology of the Nervous System. A Student's Introduction," by J. Henry Biggart. Edinburgh, E. & S. Livingstone (1936). The late Dr. S. A. Kinnier Wilson's book on "*Neurology*" (in two volumes, Edward Arnold & Co., London, 1940) was published whilst the proofs of our present edition were going through the press. It is edited by Dr. A. Ninian Bruce, Lecturer in Physiology, Neurology and Psychiatry in the University of Edinburgh, and is dedicated to the memory of our old friends, teachers and colleagues, Sir Byrom Bramwell and Dr. Alexander Bruce. It is likely to become one of the most authoritative books on Neurology in the English language, and it is a matter of regret to us not to have been able to refer to it more fully whilst writing this chapter on the Nervous System.

[2] "Illustrations of Regional Anatomy," Section I, Central Nervous System, Third Edition (1941), by E. B. Jamieson, will be found useful in following the anatomical aspects of this chapter.

SECTION I

INTRODUCTORY NOTES

Within the skull and vertebral canal, the central nervous system or neuraxis is ensheathed by **two sets of membranes,** the **dura mater** or **pachymeninx**[1] and the **pia-arachnoid mater, membrana pia-arachnoidea** or **leptomeninx,**[1] enclosing between them the potential **subdural space,** lined by endothelium and analogous to the pleural and peritoneal serous cavities.

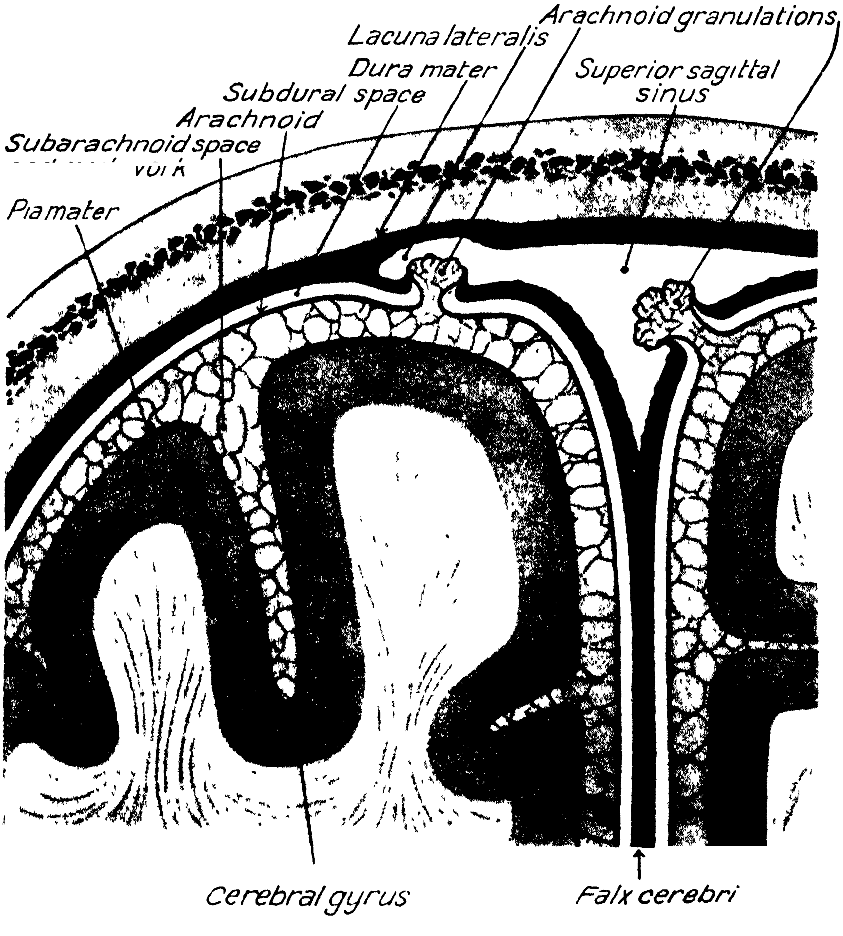

FIG. 569. Diagrammatic representation of region of vertex in coronal section, showing the arrangement of the cerebral membranes and the subdural and subarachnoid spaces, which do not communicate with each other. The arachnoid granulations or Pacchionian villi are shown projecting into the superior sagittal sinus, illustrating the main route of return of the cerebrospinal fluid into the circulation. (After Cunningham.)

The **dura mater** (**pachymeninx**) is a strong dense fibrous connective-tissue membrane which acts as the endosteal lining of the cranial bones and carries their nutrient vessels, the meningeal arteries, and at the same time acts as a protective covering for the brain and spinal cord. The dura may be regarded as being composed of two main layers which in places separate to enclose between them the various **dural venous sinuses** and **veins** which receive and carry away the blood returning from the brain. From its inner or deep aspect are given off the strong fibrous septa which partially subdivide the cranial cavity—the **falx cerebri** and the **tentorium** and **falx cerebelli,** and the small **diaphragma sellæ** which roofs in the pituitary fossa. Round the edge of the foramen magnum the outer layer of the dura is firmly adherent to the bone and becomes continuous below with the periosteum lining the vertebral canal, whilst the inner layer is continued downwards as the dural tube which ensheaths the spinal cord.

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[1] Greek μῆνιγξ, *mēninx*, a membrane, pl. μήνιγγες, *mēninges*. παχύς, *pachus* or *pachys*, thick or strong : as contrasted with λεπτός, *leptos*, thin or delicate, hence pachymeninges and leptomeninges, the hard and soft membranes.

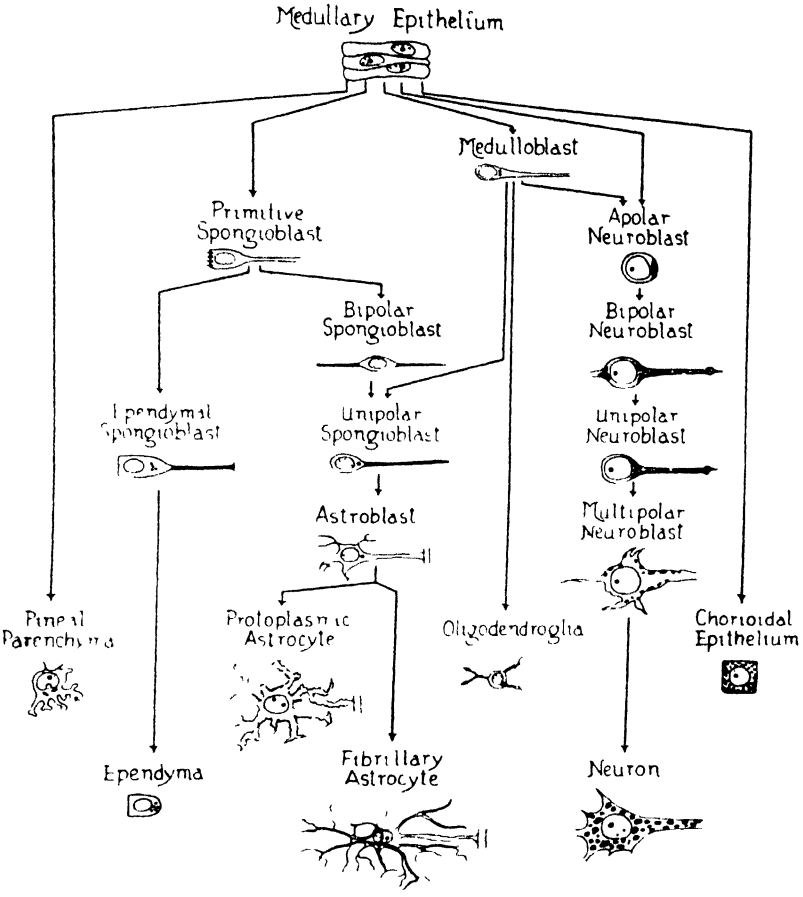

FIG. 570. Scheme recapitulating the histogenesis of the cells of the nervous system (*cf.* Figs. 192 on p. 357, and 679 on p. 1098). By courtesy of Percival Bailey, Chicago.[1]

The dura lining the vault of the skull, whilst it still, in the young subject, functions as an active formative periosteal membrane, is firmly adherent to the bone ; but, in the adult, after the bones are fully developed, it becomes less cellular and vascular and can be stripped off more readily from their inner surface, except along the lines of the sutures where it is closely adherent. As age advances, however, and also in certain pathological conditions, it becomes generally adherent. Throughout life, it is firmly bound down over the base of the skull and especially along the lines of the bony projections and around foramina, *e.g.*, where the cranial nerves and vessels leave or enter the cavity of the skull.

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[1] "Intracranial Tumors," Baillière, Tindall & Cox, London, 1933, Fig. 91, p. 212.

The **pia** and **arachnoid** (the **soft** or **lepto-meninges**) are conveniently regarded as a *single* structure—the **pia-arachnoid**—the two constituents being united by a loose connective-tissue network, in the meshes of which circulates the cerebrospinal fluid. As will be seen from the diagram (Fig. 569) on p. 951, the delicate arachnoid membrane bridges over the summits of the individual cerebral convolutions, whilst the pia-mater forms their immediate covering, dipping into each sulcus. Over the surface of the brain, subjacent to the pia, is a thin layer of condensed glial tissue (the **membrana limitans gliæ**) and the two together constitute the **surface limiting** or **pia-glial membrane,** resembling the analogous combination of **ependyma** and **glia** lining the ventricles. These, on the surface and in the interior of the brain respectively, along with the covering of the choroid plexuses and the capillary endothelium of the cerebral vessels and the lining of the perivascular spaces around these and the blood-vessels in the brain-substance, form, as it were, a "barrier" between the circulating blood and the cerebrospinal fluid. Upon the **normal** relative impermeability of this barrier, more particularly upon that of the endothelium of the capillaries—sometimes described as the **ecto-mesodermic** or **hæmato-encephalic barrier**—and on its **increased** permeability in certain pathological conditions, depend to a considerable extent the variations in the character and composition of the **cerebrospinal fluid** in health and in disease (pp. 584–5, 957, 962–3, and 995).

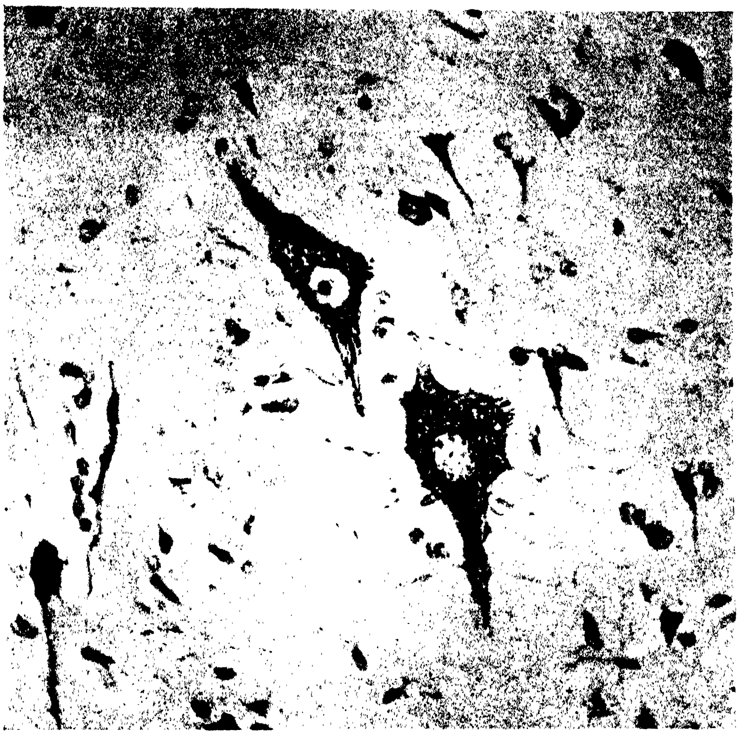

FIG. 571. *Healthy Betz-cells.* Showing nucleus and nucleolus (one cell), cell-processes and Nissl-bodies. × 300.

To understand the pathological conditions which may affect the nervous elements proper and the supporting glial tissue of the central nervous system, some knowledge of their histogenesis and normal histology is useful. Much work has been done of recent years upon this subject, particularly in its relationship to the histology and classification of tumours growing from these tissues, and any who wish to follow this important subject in detail should refer especially to the volumes and papers by Harvey Cushing and

Percival Bailey.[1] To the kindness of the latter we are indebted for permission to reproduce his schematic diagrams which will serve to remind the reader of the relevant facts. Fig. 570 recapitulates current views with regard to the development of the cells of both the **neuronal** and the **neuroglial** series (in which connection *see also* Fig. 192 in Appendix II to Chapter XIII, p. 357). The **neurones** [2] or **nerve-cells** are derived either indirectly through the as yet undifferentiated **medulloblast** (a cell which, early in development, still possesses the potentiality of differentiating into either nerve-cell or glial cell ; for tumours derived from these cells, *see* p. 1114) : or directly, through the intermediate forms of apolar, bipolar, unipolar or multipolar **neuroblast.**

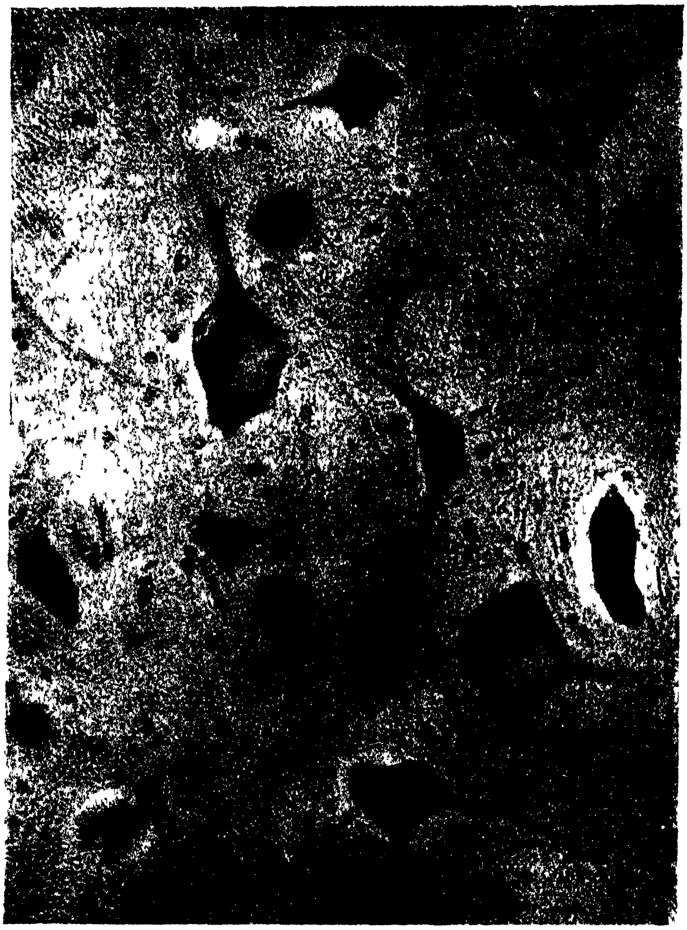

FIG. 572. *Degenerated nerve-cells.* From the anterior horn of the spinal cord in a case of Pellagra, showing eccentric position of nucleus, disappearance of Nissl-bodies, loss of processes, etc. × 300.

In its most typical form, *e.g.*, as the **multipolar nerve-cell**—for example, the pyramidal cell of the cerebral cortex or the motor nerve-cell of the anterior horns or ventral grey columns of the spinal cord—the neurone consists of cell-body and its processes. The **nucleus** is relatively large, spherical or slightly ovoid, situated more or less centrally, and possesses a definite nuclear membrane and prominent nucleolus. The rather sparse chromatin is arranged in deeply-staining granules or particles of considerable size, situated mostly peripherally just within the nuclear membrane, the whole nucleus thus having a definite clear-cut outline and structure. The **cytoplasm** contains various formed bodies such as Nissl-granules or chromidial bodies, mitochondria and Golgi-apparatus, and droplets of neutral fat, lipoids and glycogen, together with the essential **neurofibrils**—the presence of which may be demonstrated by special fixing and staining or impregnation methods.

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[1] " A Classification of the Tumors of the Glioma Group on a Histogenetic Basis," by Percival Bailey and Harvey Cushing, 1926 : and " Intracranial Tumors," by Percival Bailey, 1933, which gives detailed references to the literature. (*See also* footnote on p. 1097.)

[2] *Re* spelling of " neurone " and " axon," *see* first footnote on opposite page.

The cytoplasmic **processes** may be numerous or few, complex or simple, according to the type of cell, but each cell possesses one important process, the axis-cylinder or **axon,**[1] differing in its structure from the other processes or dendrites. It arises from a conical projection of the cytoplasm, the implantation-cone, and its most important component is the conducting nerve-fibril, of varying length according to its anatomical relations: medullated or non-medullated: ending in a terminal arborisation or, in the case of the peripheral sensory nerves, in a special sense-organ: and sometimes, during its course, giving off a number of collateral branches.

The interstitial glial supporting tissue, *i.e.*, all the non-neuronal tissue except the meninges and blood-vessels (with their supporting or perivascular connective tissue), is composed of three types of cells and their processes: (1) the **astrocytes**, (2) the **oligodendrocytes,**[2] and (3) the **microglial cells.** The first two of these arise (through the intermediate forms shown in the diagram) from the epiblastic cells of the embryonic medullary tube (*cf.* Fig. 192, p. 357); whilst the microglial cells are believed to be mesoblastic in origin, and are therefore by some writers called **mesoglial** cells (*see below*). The **astrocytes** are of two types, **fibrillary** and **protoplasmic,** and these together constitute the **astroglia** or **macroglia.** These are sometimes referred to simply as "neuroglia," but we think it preferable to include also in this general term the oligodendroglia, but not the mesenchymal microglia. The fibrillary astrocytes are found mostly in the white matter and also at the deeper part of the pia-glial limiting membrane (p. 953); but they are described as occurring also in the grey matter of the optic thalamus; whilst the protoplasmic astrocytes, which have no specific glial fibrillæ in their cytoplasm, are situated almost entirely in the grey matter. Both varieties have numerous processes ramifying amongst and supporting the nerve-elements, and each astrocyte is attached to neighbouring small blood-vessels by one or more processes each terminating in a "perivascular foot" or "sucker-like" expansion (Figs. 693 and 697, pp. 1108 and 1112), or, if near the surface of the brain, by a similar process attached to the pia.

The smaller and relatively simpler **oligodendrocytes** are most numerous in the white matter, often arranged in irregular rows between the nerve-fibres, and are believed to control the formation and nutrition of the myelin-sheaths. In the grey matter they are found also round the nerve-cells as so-called "perineuronal satellites": and in both the white and grey matter as "perivascular satellites" round the small blood-vessels. Oligodendrocytes and microglial cells do not possess "vascular sucker-feet" and have no glial fibrillæ in their cytoplasm.

The **microglial cells** or **cerebral** or **neuraxial histiocytes** are found in both grey and white matter, but are more abundant in the former, some of them also, like the oligodendrocytes, occurring as perineuronal and perivascular satellites. Early in development, these microglial cells are believed to migrate into the central nervous system along with the blood-vessels and their supporting mesoblastic connective tissue. This immigration takes place especially in certain localities which have been termed "nests" or "fountains," for example, at the points of entry of the choroid plexuses, and also around the blood-vessels and beneath the meninges related to certain nerve-tracts which are developing at about the same time as this immigration takes place. The microglial cells are thus at first amœboid, but then settle down and develop into small angular or irregularly-shaped supporting cells, with numerous complex branching processes and small deeply-staining ovoid nuclei. In many pathological conditions they retract their processes and the nucleus becomes elongated or rod-shaped—hence they are sometimes called "rod-cells" (Fig. 613, p. 1014). In this form they may remain in position, as in some chronic degenerative conditions of the central nervous system ; or they may reassume their amœboid character to act as **phagocytes,** in which capacity they often englobe and become distended with the debris of any disintegrating necrotic or hæmorrhagic matter, more especially **lipoid** material derived from the breaking-down of the myelin of damaged nerve-sheaths. They are thus transformed into so-called "compound granular corpuscles," "gitter-" (lattice- or grating-) or "foam-cells," or "myelophages" (Figs. 644–5, 659–660, and 749, pp. 1055–6, 1084–5, and 1161). In certain positions, *e.g.*, in the cerebral cortex, and in certain diseases, for example, general paresis (p. 1011), these cells are found to contain **iron-pigment,** sometimes in considerable amount—the so-called Spatz-reaction (p. 1014). Microglial cells are thus mesoblastic tissue-cells or histiocytes, comparable in their origin and functions with those of the general reticulo-endothelial system of the body, and, like them demonstrable by some of the silver-impregnation [1] and vital-staining methods.

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[1] **Neurone** and **Axon**: with regard to the spelling of these words, we follow the example of Schafer's "Essentials of Histology" 14th edition, edited by Carleton (1938), p. 173. It is there pointed out that the term "**neurŏn,**" from the Greek word *νεῦρον*, a nerve (originally a sinew, cord, fibre), may be applied appropriately to the actual **nerve-fibre**; but that the word **neurōne** was invented by Waldeyer to express the **whole nerve-cell** together with all its processes. The word **axōn,** on the other hand, is simply the transliteration of the Greek *ἄξων*, an axis, and is applied to the axis-cylinder process (Deiters), nerve-fibre process or axis-cylinder of the medullated nerves or, in the case of non-medullated nerves, to the actual nerve-fibre itself. The convenient word "**neuraxis,**" now much used in America to denote **the brain and cord,** *i.e.*, the "**central nervous system,**" *must not be confused* with these two technical terms "neurone" and "axon," here defined.

[2] **Greek** *ὀλίγος*, *oligos*, few, *δένδρον*, *dendron*, or *δένδρος*, *dendros*, a tree (with its branches).

The **ependymal cells** lining the ventricular system of the brain and central canal of the spinal cord are originally ciliated, but tend later in life to lose their cilia, though patches of ependyma may retain them, *e.g.*, in the third ventricle, aqueduct, central canal of the cord or elsewhere. Allied to these ependymal cells are the non-ciliated **choroidal epithelial cells** which develop directly from the primitive medullary epithelium ; whilst the parenchymal cells of the pineal body are also derived from the cells of the medullary tube (Fig. 570, p. 952).

In the degenerations of nervous tissue, from whatever cause, the highly specialised **nerve-cells** and **nerve-fibres** suffer most severely, and, if damaged, have little power of recuperation, and, when once destroyed, cannot themselves be regenerated. The supporting **neuroglia,** on the other hand, though sometimes affected directly by irritative toxic conditions, tends rather to proliferate in order to remove and fill the place of the dead or damaged nerve-elements. Such glial proliferation, gliosis or sclerosis may thus be **local,** for example round a chronic abscess or hæmorrhage: or **widespread,** in conditions such as general paresis ; or it may be distributed along nerve-tracts and fibres in the brain, cord, or peripheral nerves, following upon destruction of the corresponding neurone-bodies or "nerve-cells" or on interruption of the continuity of the nerve-fibres or axons with these cells of which they are integral component parts.

The ordinary mesoblastic **connective-tissue,** mostly around the blood-vessels, plays a relatively minor part in such processes, but in some circumstances undergoes varying degrees of proliferation, *e.g.*, round a chronic abscess or in and around certain varieties of tumour. In the latter instance, indeed, proliferative masses may be formed, in which both the small vessels themselves and their supporting connective tissue take part, and these masses are sometimes so characteristic in structure that they are described as "glomeruloid," from their superficial resemblance to masses of renal glomerular capillaries.

The **arteries** which supply the brain are, like other systemic vessels, under the control of the autonomic nervous system—for example, on stimulation of the cervical sympathetic, the internal carotid and its branches are constricted and the blood-flow through them consequently diminished ; whilst section of it leads to dilatation and increased flow—phenomena of importance both in the production of certain diseased conditions of the brain and in the treatment of these. The cerebral **veins** do not possess valves.

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[1] *E.g.*, by Hortega's silver-carbonate method—hence they are sometimes known as "Hortega-cells." (*See also* p. 1049.)

SECTION II

THE CEREBROSPINAL FLUID

IN HEALTH AND DISEASE

This is produced from the blood, most probably by a process of selective filtration closely akin to secretion, by the **choroid plexuses,**[1] chiefly those of the two lateral ventricles. From these it passes by the interventricular foramina of Monro into the third ventricle (Fig. 573), then by the aqueduct of the mid-brain (aqueduct of Sylvius) to the fourth ventricle. From this it percolates out by the laterally placed foramina of Luschka and the central foramen of Magendie[2] in the ependymo-pial roof of that ventricle. Through these openings the fluid passes into the cerebello-medullary subarachnoid cistern or cisterna magna, which is continuous below with the wide subarachnoid space of the spinal cord, and above communicates freely with the other basal cisterns. These in turn communicate with the subarachnoid space between the arachnoid and the pia over the general surface of the brain. From this extensive space the fluid then filters back into the blood in the dural venous sinuses and veins by way of the **arachnoidal villi** or **granulations.** Some of these villi tend to become more pronounced as age advances and also in many pathological

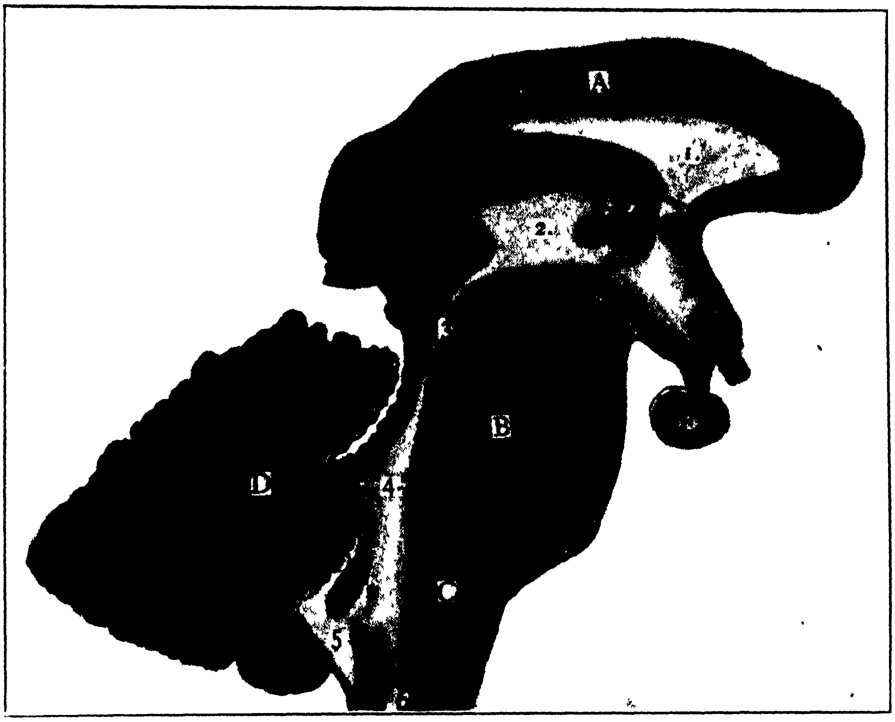

FIG. 573. Diagrammatic representation of a mesial sagittal section, through the corpus callosum and hind brain, to show:
(A) Corpus callosum: (B) pons: (C) medulla: (D) cerebellum: (E) pituitary gland. (1) Septum pellucidum between the two lateral ventricles: (2) third ventricle with foramen of Monro (F) opening into it: (3) aqueduct of Sylvius: (4) fourth ventricle, opening into (5) the cerebello-medullary cistern by the median foramen of Magendie: (6) central canal of the spinal cord. (After E. B. Jamieson.)

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[1] Halliburton in 1916 called them the "**choroid gland.**" *British Medical Journal,* 1916, ii, 610 (*see* footnote, p. 966).

[2] Anatomists and physiologists have in the past been much exercised as to the actual existence of this opening in the ependymo-pial roof of the fourth ventricle, described by François Magendie in 1828. Virchow, Bland-Sutton and others have looked upon it as an artefact, but J. T. Wilson, Emeritus Professor of Anatomy, Cambridge (*Journal Anatomy,* London, 1937, **71,** 423) and neuro-surgeons in general have no doubt that it is a natural foramen.

conditions, and those in relation to the superior sagittal sinus and its lateral lacunæ, are known as the **Pacchionian bodies** [1] (Fig. 569, p. 951).

Prolongations of the subarachnoid space are carried for a varying distance along the cranial and spinal nerves at their exits or entrances and are of importance as potential pathways of infection. In cases of raised intracranial pressure, *e.g.*, due to cerebral tumour, the tense fluid in the sheath-like channels around the optic nerves may compress the central vein and cause **papillœdema** or swelling of the nerve-head.

Another important series of prolongations or connections of the subarachnoid cavity are the **perivascular spaces of Virchow-Robin** around the arteries and veins entering or leaving the brain-substance all over its surface (Fig. 574). The vessels are thus surrounded by a double investment of pia and arachnoid, between which lies the narrow or potential perivascular space running along them for some distance, probably as far as their division into capillaries, though whether there is also a continuation of the space around the latter, perhaps communicating even with the perineuronal lymph-spaces round the nerve-cells, is still an unsettled problem.

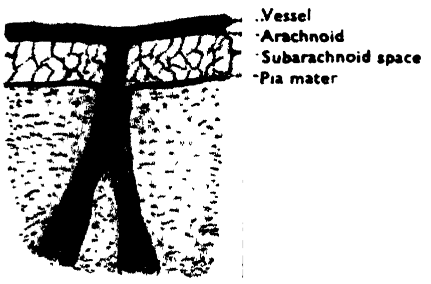

FIG. 574. Diagrammatic representation of a surface cerebral vessel passing across the subarachnoid space to enter the substance of the brain. It carries around it the perivascular Virchow-Robin space which at the surface of the brain thus opens into the subarachnoid space.

A certain amount of fluid passes *out* along these Virchow-Robin spaces into the meshes of the subarachnoid space, and, in some pathological conditions affecting brain-tissue, the products of disease may in this way be conveyed into the cerebrospinal fluid.

The chief function of the cerebrospinal fluid is to act as a protective water-bed for the delicate structures of the central nervous system, and it probably has little or no "nutritive" function, although it is believed that certain elements of the pituitary secretion are carried into the fluid in the third ventricle by way of the infundibulum.

The physical, chemical and microscopical examination of the cerebrospinal fluid provides information of much clinical value.

Normal cerebrospinal fluid is water-like, faintly alkaline to litmus (its hydrogen-ion concentration being identical with that of the blood-plasma, viz., a *p*H of 7·35 to 7·40 ± 0·02),[2] with a specific gravity of 1·006 to 1·009. In the ventricles and great subarachnoid cisterns it is practically cell-free; but, when obtained by lumbar-puncture, though still sometimes without any cell-content, one, two, or, in health, at most three, small lymphocyte-like cells per cubic millimetre may be found. Occasionally, an endothelial cell, derived from the perivascular spaces or from the surfaces of the leptomeninges, often only slightly larger than a small lymphocyte, is present. Polymorphonuclear leucocytes in the fluid are always abnormal; and, **in diseased conditions,** other varieties of cell also occur, as, for instance, phagocytic cells ("compound granular corpuscles," perhaps containing fat, englobed red corpuscles or products of inflammation), eosinophils, plasma-cells, fibroblasts, and, very exceptionally, tumour-cells. Reference will be made to pathological cell-findings under the various diseases in which they occur.

Turbidity of the cerebrospinal fluid may be due to the presence of **blood, inflammatory cells** and **bacteria,** or a combination of these. To produce a slight "smokiness" or faint "ground-glass opacity" which is *just* visible, the presence of some 500 red corpuscles per cubic millimetre is required; and a slight pinkish tint is appreciable with 1,000 and distinct with 2,000 per c.mm. When the blood is due to the accidental pricking of a vessel at the time of exploratory puncture, the corpuscles are fresh and non-hæmolysed (provided always that the needle has not been contaminated—*i.e.* is still *wet*—with spirit, ether or distilled water) and, on centrifugalisation, the supernatant fluid will, unless previously affected, *e.g.*, by pre-existent hæmorrhage, be found clear and colourless ; and, if the fluid is drawn off into two or more tubes, the corpuscles are progressively less numerous in the second or subsequent, than in the first, fraction. If the amount of such accidentally-added blood is considerable, clotting may occur. Where the blood is due to pre-existent subarachnoid hæmorrhage, *e.g.*, from fracture, leakage from an aneurysm, rupture of an intracerebral hæmorrhage into the subarachnoid space, or bleeding from a tumour, varying degrees of lysis of the corpuscles and consequent tinting of the fluid itself with the extravasated hæmoglobin tend to supervene after a few hours, but, even with considerable amounts of such hæmorrhage, clotting *in vivo* is usually prevented by the occurrence of fibrinolysis.

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[1] *See* footnote on p. 1065.

[2] *See* footnote on p. 587.

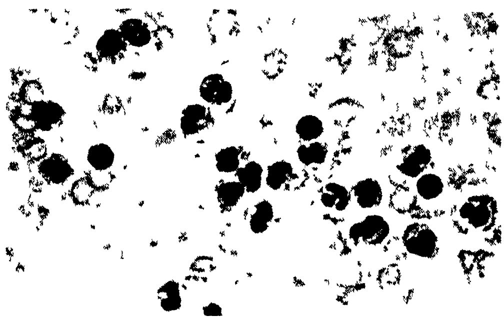

FIG. 575. Case of fractured skull in attempted suicide by a woman aged twenty nine A considerable number of polymorphonuclears, together with a few small lymphocytes, were present in a slightly blood-stained fluid containing numerous "shells" of hæmolysed red corpuscles. An examination of the cerebrospinal fluid made two months previously had given a normal finding, with only two small lymphocytes per c.mm. No organisms were found in the fluid, and the patient recovered from the injury. (Fresh-wet preparation of centrifugalised deposit in toluidin blue. × 400.)

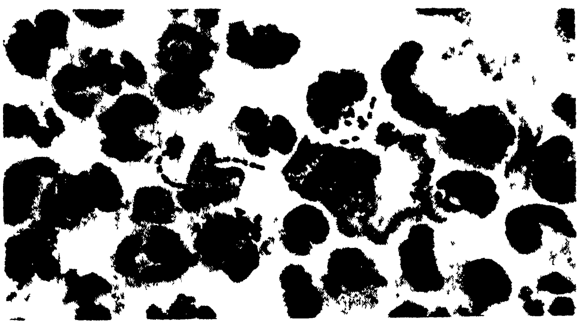

FIG. 576. Polymorphonuclear exudate in a case of acute purulent meningitis due to *Streptococcus mucosus*, a not uncommon organism of middle-ear and sinus infection. (Centrifugalised deposit stained by Leishman's method. × 1,250.)

Blood undergoing hæmolysis within the subarachnoid space, *e.g.*, after fracture, is usually accompanied and followed by some slight or moderate irritative increase in the number of polymorphs (Fig. 575), but this soon passes off unless micro-organisms also gain entrance.

Some 500 lymphocytes or 300 polymorphonuclear leucocytes per cubic millimetre will cause a *just* appreciable fine " ground-glass " turbidity of the fluid.

Moderate, and in some cases considerable, numbers of **polymorphonuclear cells** may be found along with the characteristic **small lymphocyte-like** and other **mononuclear cells** in the acute stages of tuberculous and syphilitic infection of the leptomeninges, and may also follow the injection of lipiodol and other radio-opaque substances, or be found even after the insufflation of air or oxygen as a preliminary to radiological examinations. The presence of **polymorphs in larger numbers** is, however, most typical of meningitis produced by pyogenic organisms such as meningo-, pneumo-, strepto- or staphylo- cocci. The finding of neutrophil polymorphonuclear leucocytes in numbers sufficient to cause a naked-eye appearance of " frosted glass " does not of necessity imply the presence of micro-organisms in the fluid. A not uncommon example of this is the reaction of the meninges which may accompany a mastoid infection in which the organisms may not be demonstrable in the subarachnoid space; the fluid may be turbid, and yet viable bacteria may not be found on culture. Considerable numbers of polymorphs may be found in the fluid as a result of necrotic changes in gliomatous or other tumours if these involve the surface of the brain.

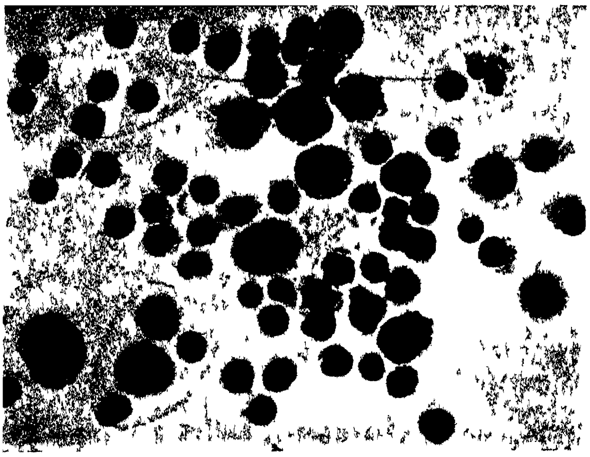

FIG. 577. *Lumbar-puncture fluid:* a subacute exudate becoming chronic in a case of so-called " chronic staphylococcal granuloma," supervening, in this particular case —and a rare occurrence—upon compression of the cervical enlargement by a herniation or prolapse of one of the intervertebral disks in a man aged forty-two. Small lymphocyte-like cells predominate, with all intermediate stages between them and the considerable numbers of small mononuclear (endothelial) cells present, together with a few polymorphs and an occasional plasma-cell. (Fresh-wet preparation of centrifugalised deposit in toluidin blue. × 800.)

A slight or moderate increase of the **small lymphocyte-like cells**—perhaps 5 to 50 cells per c.mm.—is common in many chronic infective and irritative conditions, as for instance cerebral abscess, tumour, disseminated sclerosis and neurosyphilis. A moderate increase is frequent in herpes zoster, mumps, acute anterior poliomyelitis, epidemic encephalitis and the encephalitis complicating the specific fevers, spirochætosis icterohæmorrhagica, and also in rabies and trypanosomiasis. A marked lymphocytic increase is characteristic of tuberculous meningitis (p. 994) : benign lymphocytic choriomeningitis (p. 1000) : and syphilis in its more acute and sometimes in its more progressive chronic forms (p. 1010).

Larger mononuclear cells, some perhaps hæmatogenous, but most of them in all probability derived from endothelial cells lining the leptomeninges and perivascular spaces, are commonly found along with, and to a large extent giving rise to, the smaller lymphocyte-like cells. They increase in numbers and gradually replace the polymorphonuclear neutrophil leucocytes of an acute meningitis which is subsiding (p. 987). "**Compound granular corpuscles**" ("Gitterzellen" or "foam-cells," pp. 955–6 and 1049 : and Figs. 644–5, pp. 1055–6 : Figs. 659–660, pp. 1084–5 : and Fig. 749, p. 1161) are derived largely from the microglial cells of nervous tissue which have become amœboid and actively phagocytic and may find their way into the fluid.

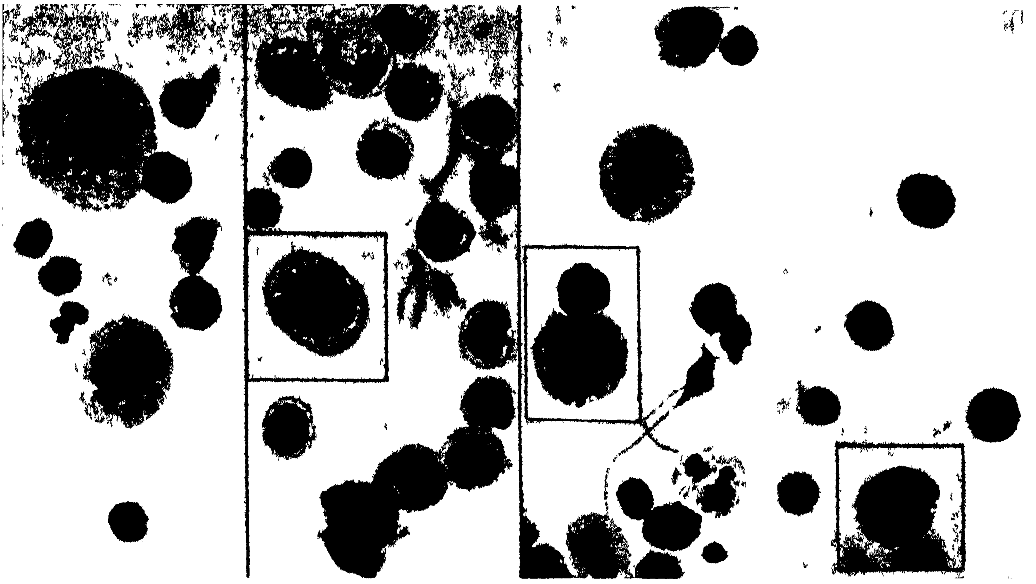
(1) (2) (3) (4)

FIG. 578. *Meningococcal meningitis* fresh-wet films from three W.E.H. cases (1) a girl aged ten years : (2) a baby aged six months : and (3) and (4) a man aged twenty-three years, all of whom recovered under chemotherapy with "soluseptasine." A series of films from these cases showed, in the earlier stages, *larger*, and, in the later, *smaller*, *endothelial cells in mitotic division*, with the formation of progressively smaller "daughter-mononuclears." The smallest cells of the series are indistinguishable from "small lymphocytes." (The juxtaposition of the small lymphocyte and mitotic cell in the inset in (3) is merely accidental) Fresh wet toluidin-blue preparations [1] of centrifugalised deposits. × 1,000.

Plasma-cells (p. 29) are frequently found in the cerebrospinal fluid, for example, in neurosyphilis and tuberculous meningitis.

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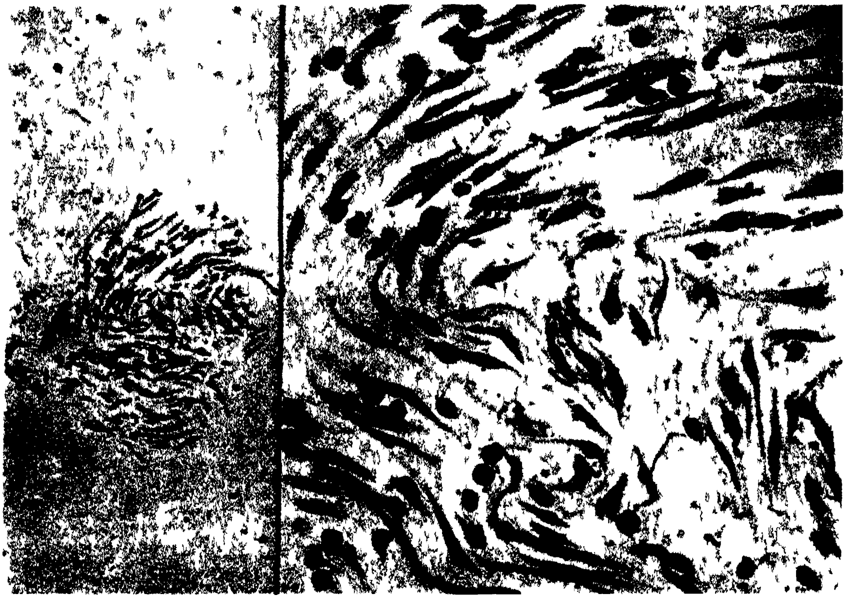
[1] The process of transition in the type and size of the cells in these exudates can be watched and studied under almost "experimental" conditions in the successive puncture-fluids. Owing to the efficacy of modern chemotherapy (see footnote on p. 985), post-mortem material, only too abundant during the last war, is now much less available ; but the examination of *fresh living cells*, such as those illustrated above, is equally, or perhaps more, helpful and instructive for the investigation of their probable nature and origin.

Fibroblasts (Fig. 579), or young spindle-shaped connective-tissue cells associated with the formation of early adhesions, are occasionally found in the fluid in chronic inflammatory conditions.

Tumour-cells are rarely identifiable with certainty as such, but may sometimes be recognised where medulloblastomas or other neoplasms have invaded the leptomeninges (p. 1099 *et seq.*).

Total Coagulable Protein. The amount of this in **normal** cerebrospinal fluid varies, not only with the **age** of the patient, but also with the **level** at which the specimen is drawn off.[1] It is least in amount in specimens from children and from the ventricles, and greatest in elderly patients and in lumbar-puncture fluids, whilst cisternal fluids give intermediate readings. Thus, in the normal ventricular fluid from a child, it does not usually exceed 5 mgr. per 100 c.cm.; whilst in lumbar-puncture fluid from the young to middle-aged adult it may be from 15 to 30 mgr. per 100 c.cm.; and in the fluid obtained from the lumbar theca in elderly patients, may rise to almost double that amount, though these larger figures are suggestive of the possible presence of some degree of vascular degeneration. Most of the coagulable protein is in the form of **albumin**; whilst **globulin,** owing to the larger size of its molecules, is less diffusable, and the minimum trace of it in the form of pseudoglobulin permitted to pass through the normal endothelium of the capillaries of the healthy brain substance and choroids is insufficient in amount to give any visible reaction with the ordinary routine clinical tests, and in a normal



(A) × 100. (B) × 400.

FIG. 579. A clump of young fibroblasts in the cerebrospinal fluid from a case of general paresis, indicating the formation of early adhesions. Moderate numbers of small lymphocyte-like cells of the general exudate characteristic of the chronic syphilitic lesion are also present. (Fresh wet preparation of centrifugalised deposit in toluidin blue.)

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[1] Carnegie Dickson, "The Examination of the Cerebrospinal Fluid," *Medical Press and Circular*, 1937, **194,** *Supplement* on "*The Brain,*" *p. xviii,* and continued on pp. 75 and 597.

fluid it is therefore reported as " not present in excess." The ratio of albumin to globulin in health is usually regarded as about 8 to 1.

Increase of the total coagulable protein occurs in many pathological conditions. In some diseases, the normal ratio may be approximately maintained, as where the lesion is predominantly of a mechanical nature ; but in others the globulin shows a greater proportional increase, for example, when the permeability of the barrier between the blood and the fluid (pp. 584 and 953) is increased by irritative, infective or degenerative lesions, and the larger globulin-molecules are allowed to pass through more easily. This is seen most characteristically in general paresis and disseminated sclerosis, in which the globulin is increased in amount, whereas the total amount of coagulable protein is only slightly increased or even remains unaltered.

Mention may be made here of the great rise in protein which occurs in the "**loculation-syndrome of Froin**", brought about by a localised obstruction of the spinal subarachnoid space ("**spinal block**"). It can be caused by compression from outside the meninges by tuberculous diseases of the spine, herniation or protrusion of the intervertebral disks, thickening of the ligamenta flava, tumour, epidural abscess, or by inflammatory diseases or neoplasms of the membranes, spinal cord or nerve-roots. The fluid in the portion of the theca *below* the obstruction is cut off from the normal course of the cerebrospinal circulation and the protein-content rises considerably and may come to exceed even 3 per cent. (3,000 mgr. per 100 c.cm.). Such a fluid frequently undergoes spontaneous coagulation after withdrawal. **Xanthochromia** [1] is often present, the colour varying from pale amber to dark orange or even orange-green, from the presence of hæmoglobin or some of its derivatives.

Glucose to the amount of 40–80 mgr. per 100 c.cm. is present in the normal fluid, as compared with, say, 80–100 mgr. per 100 c.cm. in the blood. The amount is increased in diabetes mellitus ; whilst a **fall** of the sugar in the fluid below 40 mgr. (unless the patient is suffering from *hypo*glycæmia such as may occur in " hyperinsulinism," pp. 799–800 *et seq.*) is suggestive of a probable **meningitis, tuberculous** (in which it is usually below 30 mgr. and may decrease to 20 or perhaps 15 mgr.) or **suppurative** (in which it may be not merely diminished but often completely absent). This fall in the level of the sugar in **bacterial meningitis** is usually accompanied by a corresponding **rise** in the amount of **lactic acid** derived from the breaking-down of the sugar, a process apparently often in direct proportion to the number of cells in the inflammatory exudate, as well as due to the action of certain saccharolytic micro-organisms, such as *Bacterium coli* (*cf.* 995). In **viral infections,** on the other hand, and also in **syphilitic** lesions, the percentage of sugar remains comparatively unaffected.

Chlorides. The amount of these in the cerebrospinal fluid, estimated as sodium chloride, is always greater than in the circulating blood-plasma, a phenomenon to be explained as probably a provision to keep the fluid isotonic with the blood, the increased amount of chlorides compensating for the much smaller protein-content of the fluid. The percentage of chlorides in the cerebrospinal fluid is normally 720 to 760 mgr. per 100 c.cm., as compared with only 570 to 620 mgr. in the blood-plasma. An increase above 760 mgr. per 100 c.cm. in the fluid may be associated with cardiac or renal insufficiency; whilst a **fall** is usual in **bacterial meningitis.** In tuberculous meningitis (p. 995), the fall in chlorides is characteristic—perhaps to 500 mgr. or less per cent—*i.e.*, lower than in any other known pathological condition. In "**benign**" **lymphocytic choriomeningitis** (pp. 116 and 1000) and other **viral diseases,** including poliomyelitis, the chlorides, as well as the sugar, are *not* reduced in amount. In the **alkalosis**[1] which develops in some cases of gastric and duodenal ulcer, and in pyloric and intestinal obstruction, and especially after vigorous therapy with alkalies, the blood, and consequently the cerebrospinal fluid, become abnormally alkaline; and there is increase in blood-urea and diminution in blood-chlorides; in the urine, chlorides and ammonia are almost absent; and **in the cerebrospinal fluid** there is a corresponding **rise in urea** and **diminution in chlorides,** the latter phenomenon having also been noted in cases of Addison's disease.

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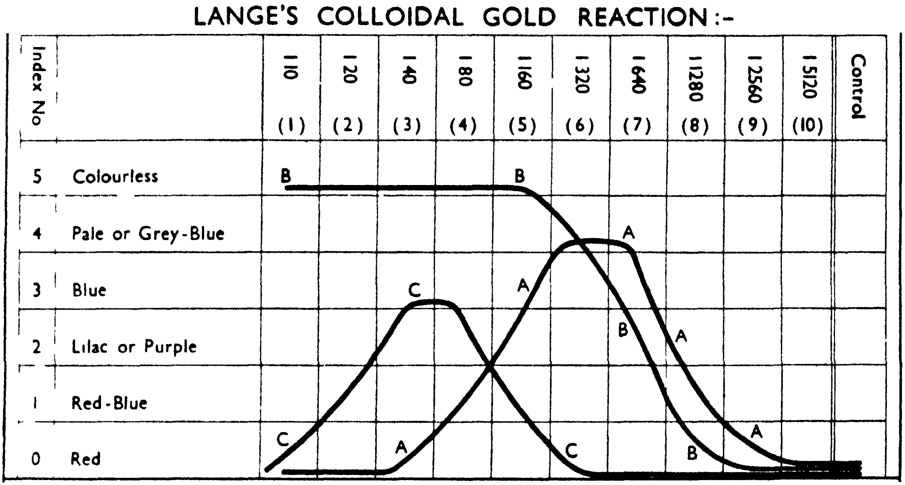
[1] Greek ξανθός, *xanthos, literally* yellow of various shades, often with a tinge of red : χρῶμα, *chrōma,* tint or colour.



Typical Lange Curves -

(AAA) Meningitic Field, which would be recorded as 0001243200

(BBB) Paretic Field, ,, ,, ,, ,, ,, 5555542000

(CCC) Luetic Field, ,, ,, ,, ,, ,, 0133100000

FIG. 580. Chart to illustrate the three main types of Lange's colloidal gold curve.

Colloidal Reactions. Numerous "colloidal reactions" have been devised for the diagnosis of certain pathological conditions of the cerebrospinal fluid, but the most generally used of these is **Lange's Colloidal-Gold Reaction.**

Detailed descriptions of this will be found in special works on Clinical Pathology, and it is sufficient here to mention that three characteristic types of reaction are obtained with the ruby-red colloidal-gold solution employed. The **first-zone** or "paretic" type of curve—(BBB) in the accompanying figure—is seen characteristically in general paresis and in the more active phases of disseminated sclerosis; whilst the **mid-zone** "luetic" type (CCC) occurs especially in tabes dorsalis and meningo-vascular syphilis. The **end-zone** or "meningitic" type of reaction (AAA) is, as the term implies, obtained especially in cases of meningitis, but may be found also where there is a large increase of coagulable protein (p. 963) and in certain cases of tumour.

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[1] "The Cerebrospinal Fluid in Alkalosis," by Herbert Agar and Ian Macpherson (Leeds). *Lancet,* 1940, i, 171.

SECTION III

DISEASES OF THE MEMBRANES AND VENTRICLES[1]

Cerebrospinal Rhinorrhœa and analogous conditions. Leakage of the fluid into, and its discharge, sometimes in large quantities, from, the nose, may occur after fracture of the base of the skull involving the cribriform plate and ethmoidal sinuses or the walls of one of the frontal sinuses; and it also occasionally follows surgical interference with these. Infective organisms may gain entrance and produce a purulent meningitis, cerebral abscess or suppurative ependymitis (Figs. 643–5, pp. 1054–6). More rarely, the escape of cerebrospinal fluid occurs apparently "spontaneously," mostly in adults, the leakage taking place in all probability along the sheaths of the olfactory nerves. In such cases, air sometimes enters the cranial cavity from the forcible blowing of the nose, secondary bacterial infection being then also likely to supervene. (See also Chapter XVII, p. 502.)

Accidents or surgical operations involving other parts of the cranial membranes or spinal theca are sometimes similarly followed by leakage of the cerebrospinal fluid into the surrounding tissues. The severe headache which sometimes follows lumbar puncture is generally due to such leakage, especially if a large needle has been used and its cutting bevel introduced transversely, instead of *longitudinally*. The latter direction is always advisable, so as to avoid cutting across the longitudinally-arranged fibres of the dura and producing the little gaping buttonhole-like openings in the membranes sometimes found *post mortem*. The fluid may also find its way externally through some wound or sinus, or by a natural passage such as the ear. Here again, secondary septic infection is liable to occur.

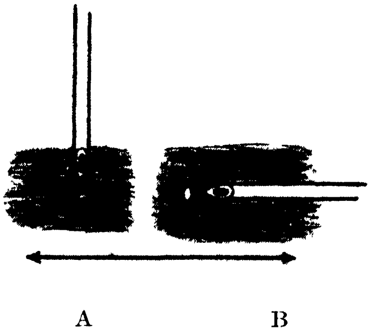

FIG. 581. Lumbar puncture. If the cutting edges of the bevel are held in the long axis of the patient's body, *e.g.*, with the flat or ground surface of the bevel downwards towards the bed or couch), the small longitudinal puncture closes automatically as shown in the left-hand diagram (A); but if, as in the right-hand figure (B), the bevel is held transversely to the patient's body, the fibres of the dura, which are mainly longitudinal, are divided transversely and the puncture tends to "gape" and remain open, leading to subsequent leakage of the cerebrospinal fluid.

ACCUMULATIONS OF CEREBROSPINAL FLUID IN THE MEMBRANES AND CAVITIES OF THE BRAIN:—

ŒDEMA. Apart from the accumulation of the cerebrospinal fluid in the subarachnoid space as part of the phenomena described below under hydrocephalus, œdema of the membranes of the brain, especially the pia-arachnoid, occurs along with œdema elsewhere in some cases of nephritis and heart-disease (p 179). It is by no means uncommon to find only general œdema of the membranes and brain-substance in cases which clinically have exhibited symptoms—especially if supervening during the course of nephritic or allied diseases—suggesting some localised cerebral lesion such as hæmorrhage, thrombosis or tumour; whilst, on the other hand, localised œdema may occur as a complication in and around cerebral tumours and traumatic and other lesions, especially when these are the seat of degenerative and necrotic changes.

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[1] See explanatory note on first page of this chapter (p. 950).

HYDROCEPHALUS is a condition in which there is an excess of cerebrospinal fluid within the cranial cavity. It may affect any part of the ventricular, subarachnoid and other positions in which the cerebrospinal fluid is normally present.

1. **Compensatory** or **Retraction-Hydrocephalus.** This supervenes in cases of shrinking or atrophy of the brain, for example, in general paresis, senile dementia, cerebral arterial degeneration and analogous conditions. The cerebrospinal fluid accumulates in the meshes of the pia-arachnoid and in the ventricles as a purely **passive** phenomenon, unaccompanied by any increase of intracranial pressure. A similar passive accumulation of fluid is found in any form of congenital hypoplasia, general or localised.

2. **Hypertensive Hydrocephalus** or **Hydrocephalus proper.** This may be due to one or more of the following factors :—

   (i) Over-active secretion by the " choroidal glands." [1]
   (ii) Obstruction to the cerebrospinal circulation, more especially at any of the narrower parts of the pathway.
   (iii) Imperfect reabsorption of the fluid into the blood-stream by way of the arachnoidal villi.

(i) Some degree of **over-production** of the cerebrospinal fluid occurs where there is obstruction to the venous return from the choroid plexuses, *e.g.*, such as is produced by compression or thrombosis of the great cerebral vein of Galen or of the straight sinus into which it flows. Active over-production of the fluid was formerly believed to be the main factor in the causation of so-called " primary " or congenital hydrocephalus, but this form of the disease is now regarded as due more probably to some lesion leading to obstruction, or in some cases to deficient reabsorption of the fluid into the blood.

(ii) **Obstruction** to the circulation of the cerebrospinal fluid itself at any part of its pathway will produce dilatation *above* the site of the obstructing lesion. Non-development of one foramen of Monro or its closure by tumour or inflammation will lead to an accumulation of the fluid in the corresponding lateral ventricle ; whilst, if both foramina are congenitally absent or have become obstructed or obliterated, for example by tumour involving the third ventricle, the resulting dilatation will be bilateral. If the obstruction is situated in the aqueduct of the mid-brain (the aqueduct of Sylvius), from non-development, ependymitis, or from compression or obliteration by tumour, the third ventricle, together with the lateral ventricles, will be dilated. A hydrocephalus of this type may arise also in some cases of concussion, *e.g.*, from falls upon the buttocks, causing bruising of the brain-stem against the rigid horseshoe-edge of the incisura of the tentorium cerebelli, with consequent œdematous swelling around, and closure of, the aqueduct (Fig. 573, (3), p. 957). If the obstruction affects the foramina of Magendie and Lushka in the ependymo-pial roof of the fourth ventricle, that cavity itself, along with the aqueduct, and the third and lateral ventricles, will be dilated.

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[1] The choroid plexuses have been so described by Harvey Cushing in his Cameron Lectures on " The Third Circulation and its Channels " (*Lancet*, 1925, **ii**, 851), and also by Halliburton. The latter, in his paper, " The Possible Functions of the Cerebrospinal Fluid," *British Medical Journal*, 1916, **ii**, 609, basing his verdict upon both his own work and that of Cushing and Weed, wrote : " We can have no hesitation in proclaiming that cerebrospinal fluid is a true secretion arising in a definite glandular structure." The term **choroidal** or **choroid gland** might therefore conveniently be adopted, whether the production of the fluid be regarded as a " secretion " or as a " selective filtration."

In these various forms of **obstructive hydrocephalus,** flattening of the convolutions, ballooning of the floor of the third ventricle and infundibulum, with possible compression of the pituitary body and optic commissure, may ensue. The possible results of such compression of the pituitary are described on pp. 808 *et seq.*, and 989–990 (*see also* Figs. 472 and 595 and, pp. 817 and 989). The more central portions of the under surface of the cerebellum and the adjacent parts may be so impacted around the medulla into the foramen magnum—as the so-called "**pressure-cone**" (Fig. 582) —that the foraminal exits from the fourth ventricle are obstructed, with resulting acute hydrocephalus (compare also p. 984).

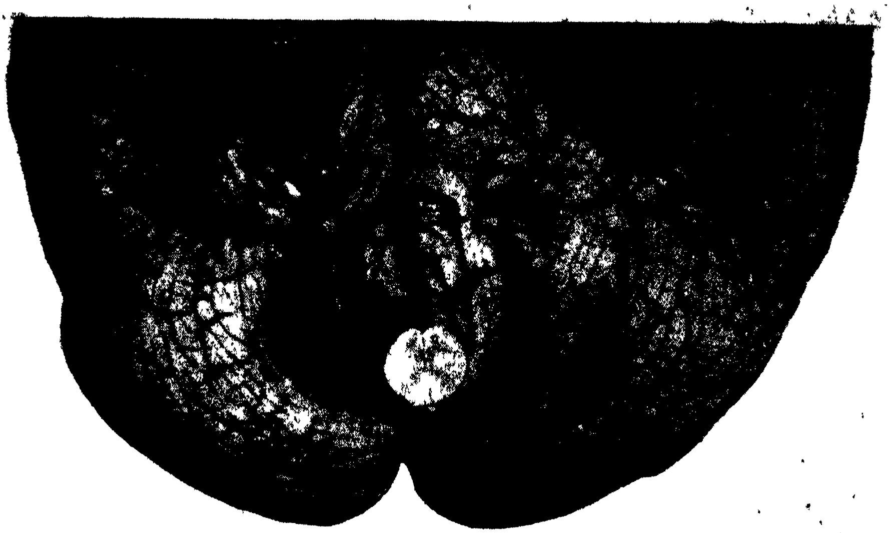


FIG. 582. Medulla and under surface of cerebellum showing "*pressure-cone*" from impaction into foramen magnum due to increased intracranial pressure in a case of cerebral tumour in a man aged forty-nine.

If, in such cases of blockage of the foramina, a solution of a suitable anilin dye is injected into the cerebrospinal fluid in one of the dilated lateral ventricles, it will *not* find its way out into the basal subarachnoid cisterns, etc., and down into the spinal theca; whereas, with no such obstruction, the fluid will, on lumbar puncture, be found coloured by the dye within a few minutes of the intraventricular injection. These first-mentioned varieties of hydrocephalus are, therefore, described as "**non-communicating,**" as contrasted with other forms of hydrocephalus brought about by extra-cerebral lesions such as an arachnoiditis which has produced a widespread obliteration of the subarachnoid space, for example, over the convexity of the hemispheres, but in which the foramina in the ependymo-pial roof of the fourth ventricle are *not* blocked.

If the almost complete subdivision of the cranial cavity by the tentorium cerebelli is borne in mind, it will be understood that **obstructive adhesions** at the level of the "narrows" of the **incisura tentorii** (where it embraces the mesencephalon or brain-stem connecting the contents of the posterior cranial fossa with the cerebrum) are of special importance in relation to the production of this form of hydrocephalus. Extensive obliterative adhesions of the subarachnoid space may follow upon subarachnoid hæmorrhage, *e.g.*, from birth-injuries; or they may be the result of a widespread arachnoiditis (p. 1021).

(iii) **Occlusion of the arachnoidal villi** (Pacchionian bodies, etc.) by chronic inflammatory processes or by their invasion and obliteration by tumour-cells will also interfere with the normal process of reabsorption of fluid through them into the cerebral venous sinuses and veins, a result which may also be brought about by **thrombosis** of the blood within these channels themselves (Fig. 569, p. 951).

These varieties of hydrocephalus due to obstructive lesions of the subarachnoid space are of "**communicating**" type, for, as explained above, the colour of the dye injected into one of the lateral ventricles will find its way down the spinal theca within some five or ten minutes and be demonstrable on lumbar puncture, whilst the pressure of the fluid in the ventricles and in the lumbar theca will, with the patient in the horizontal position, be equal, and increased in equal degree. (*See* pp. 1021–22.)

Hydrocephalus has also been classified into **congenital** and **acquired** forms.

(*a*) **Congenital Hydrocephalus.** In congenital hydrocephalus there is gradual dilatation, especially of the lateral ventricles, with corresponding thinning of the brain-substance and of the bones of the skull, the latter being unduly separated and closure of their sutures delayed or prevented. The frontal bones are pushed forwards so that the forehead rises perpendicularly or overhangs the eyebrows, the parietal bones bulge laterally, and the occipital bone is pushed backwards. In spite of the great thinning of the brain-substance and the pressure exerted on it, its functions may to a considerable extent be retained. Often, however, the definitely hydrocephalic child is mentally enfeebled. The lateral ventricles undergo the greatest degree of dilatation, but the foramina of Monro, the third, and—if the obstruction is not situated in the aqueduct of the mid-brain (the aqueduct of Sylvius)—the fourth, ventricle, as well as the aqueduct itself, may also be dilated (*cf.* Fig. 573, p. 957: and Figs. 584–5 opposite). Their ependymal lining-membrane is usually thickened and may appear somewhat granular. The accumulated fluid, which sometimes amounts to a litre or more, is clear, watery and of low specific gravity. Microscopically, the brain-substance shows varying degrees of compression, the deeper white matter especially being affected, with destruction of myelin and other degenerative changes.

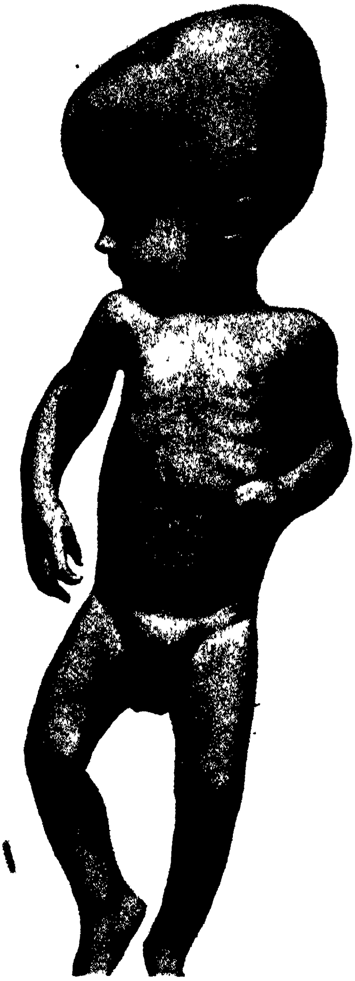


FIG. 583. Congenital hydrocephalus in male infant, aged four months.

Congenital hydrocephalus may be accompanied by defects in the neural

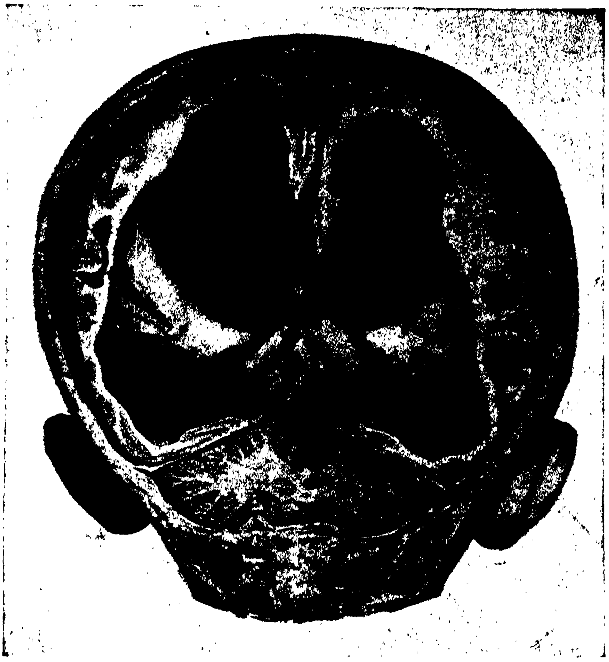


FIG. 584. Coronal section through the cranium and brain of a case of chronic hydrocephalus, showing extreme distension of the lateral ventricles. (From the Pathological Museum, University of Sheffield.)

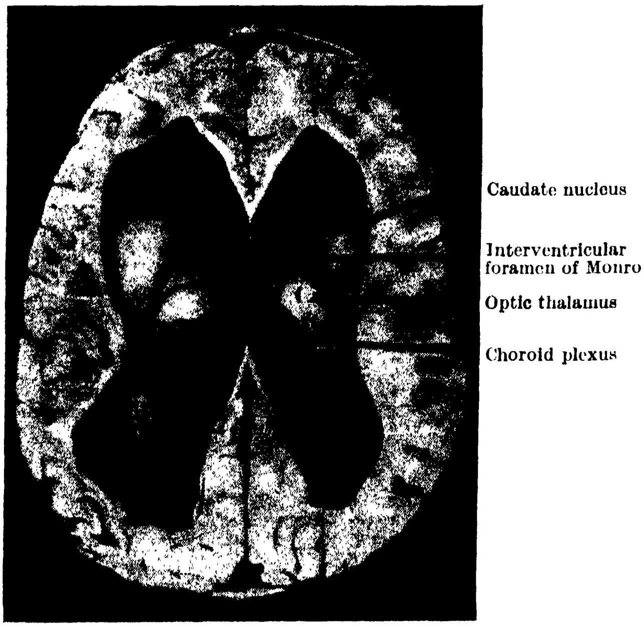


FIG. 585. Congenital hydrocephalic brain: horizontal section through the hemispheres showing the anatomical structures on the floors of the lateral ventricles exposed in an exaggerated degree by the chronic dilatation. (Sir Harold Stiles and Carnegie Dickson's case, R.H.S.C. Ed.[1])

[1] *British Medical Journal*, 1898, ii, 335 (*cf.* footnote on p. 459).

arches of the vertebræ and varying degrees of protrusion of the cord and its membranes (*see under* Spina Bifida, p. 1066).

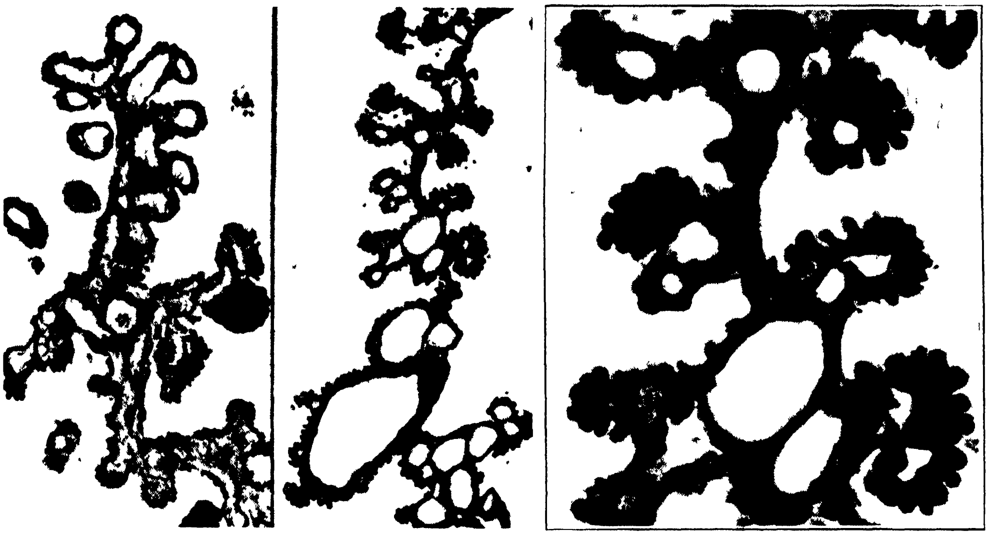
(*b*) **Acquired Hydrocephalus.** A basal meningococcal, syphilitic or other form of meningitis may cause the sealing up of the foramina in the roof of the fourth ventricle (*see* Fig. 573, p. 957), or may produce adhesions around the base of the brain and cerebellum, and so lead to the production of acquired hydrocephalus. In meningococcal cases this may occur during the active stage of the disease, when the accumulation of fluid is aggravated by the inflammatory reaction (transudation of lymph, etc.), which involves the choroid plexuses and the lining-membrane of the ventricles. A subsidiary but important phenomenon aiding in the production of hydrocephalus, already described (p. 967), is the formation of the so-called " **pressure-cone** " (Fig. 582, p. 967) from the impaction of the medulla and neighbouring portions of the cerebellum into the foramen magnum, due to increase of intracranial, and more particularly of intracerebral, pressure or to increase of the bulk of the cranial contents from congestion or œdema. Hydrocephalus itself, once started, has, as already noted, a similar result, the two conditions, hydrocephalus and impaction, mutually aggravating each other. Some cases of acute hydrocephalus are thus produced without actual obliterative sealing-up of the foramina in the ependymo-pial roof of the fourth ventricle by the inflammation, and may take place during the active disease (in which case, and especially in meningococcal or cerebrospinal fever, the causal organisms are practically always present in the ventricular fluid) ; or, from the subsequent occurrence of fibrous adhesions, the hydrocephalus may supervene during convalescence. Acquired hydrocephalus due to obstruction of some part of the cerebrospinal pathway by tumour may be of all degrees and has already been mentioned on p. 966.

DISEASES OF THE MEMBRANES[1]

(With Ventricular Ependyma and Choroids)

CONGENITAL ABNORMALITIES, *e.g.*, **Meningoceles,** etc. (p. 1065).

DEGENERATIVE CHANGES of the nature of **fibrous-tissue overgrowth,** with associated thickening of the skull, are seen in the dura and pia-arachnoid in old people, in chronic mental disease, and in alcoholics; and the dura may become more firmly adherent than normal to the bone, or adhesions may form between the dura and the subjacent pia-arachnoid, and be followed, perhaps, by **calcification** and the production of **plaques.** A not uncommon site of such calcified plates is the falx cerebri, but they are of more frequent occurrence in the leptomeninges of the spinal cord (Fig. 751, p. 1165).



A × 100. B × 100. C × 275.

FIG. 586 (A) and (B). Low-power sections of choroid plexus to show general structure.

(A) From an elderly male, showing some slight commencing increase in the fibrous tissue of the cores between the central capillaries and the surface choroidal epithelial cells. Two small areas of commencing calcification or particles of "brain-sand", corpora arenacea, are shown, one towards the right margin, the other cut across by the lower edge of the photograph.

(B) From a child aged two with chronic hydrocephalus. The central vessels are dilated and there is slight "beading" of the surface epithelium, but little or no fibrous thickening.

(C) Higher-power view of central area of (B) to show the "beaded" surface epithelium and the dilated central vessels.

Hæmatoxylin and eosin.

Sometimes the thickening, particularly of the pia-arachnoid, is widespread; or, in other cases, localised fibrous areas, especially at the points of intersection of the sulci, are produced, and these may simulate tubercle-granulations. If examined closely, however, their edges are seen to be rather indefinite, merging gradually into the surrounding tissue. When distributed in a more patchy manner they may resemble the cloudy appearance of early purulent meningitis, but can usually be distinguished from the latter by their more pearly-white lustre and, on running the finger or the back of a knife firmly over them, by their not being easily displaced, as is an early inflammatory exudate. In chronic forms of mental disease, especially general paresis, there is usually thickening of and adhesions between the membranes themselves, and also between the membranes and the cortex (p. 1011 *et seq.*). Associated with these degenerative changes in the membranes, the ependymal lining of the ventricles may show granular thickening and the choroid plexuses become the seat of fibrosis and the formation of an excess of corpora arenacea or particles of " brain-sand " (pp. 1122–25 and Figs. 712 to 714, pp. 1123 and 1124).

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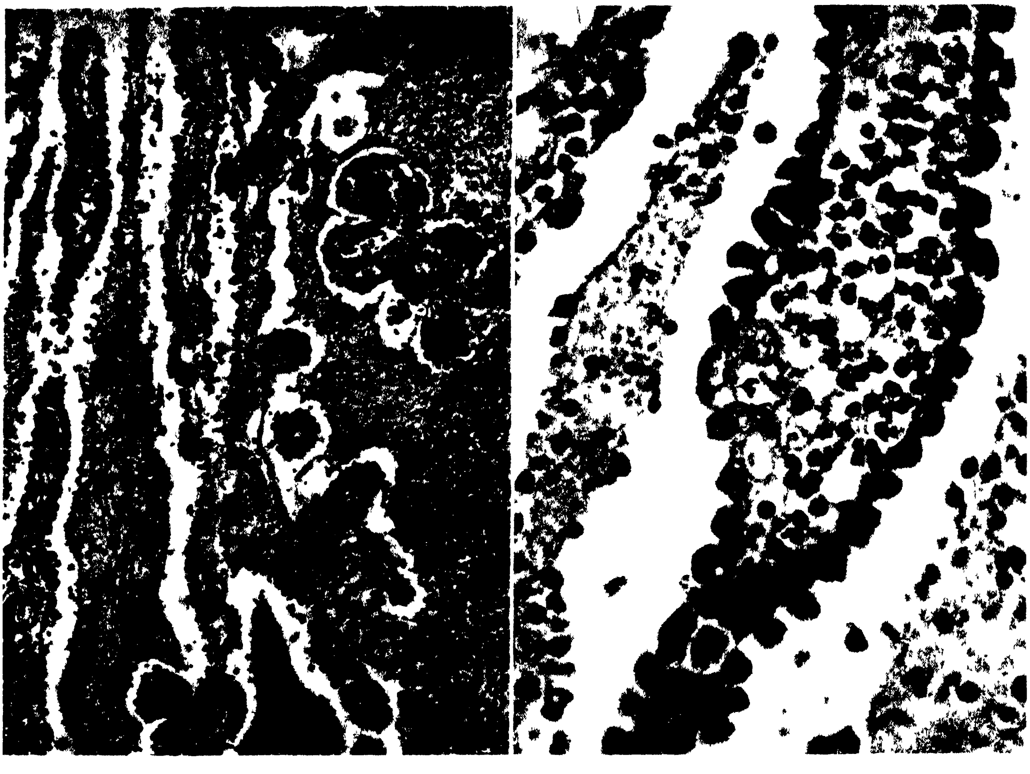
[1] See explanatory note in third paragraph of this chapter (p. 950).

Other Lesions of the Choroid Plexuses :—

Acute suppurative choroiditis is found in meningococcal and other infections, and in Fig. 587 are illustrated the appearances in an acute infection of the ventricles with *Staphylococcus aureus*, from the same case as Figs. 643 and 644–5, pp. 1054 and 1055–6. We are unable to illustrate the changes in **acute lymphocytic choriomeningitis** (pp. 116 and 1000), as we have not encountered a fatal case of the disease. A non-infective, and sometimes hæmorrhagic, and even "pseudo-suppurative," endoventriculitis may supervene after the injection of certain



(A) × 85. (B) × 350.

FIG. 587. *Acute suppurative choroiditis* in a man aged twenty-nine years, showing a fibrino-purulent inflammatory exudate in and around the choroid plexus of one of the lateral ventricles, due to infection with *Staphylococcus aureus*. Note the beaded swelling of the surface epithelial cells and the infiltration of the cores of the villi with polymorphs. Hæmatoxylin and eosin.

radio-opaque substances (*cf.* p. 1059 : and Fig. 628, p. 1037). **Tuberculosis** of the choroid is illustrated in Fig. 599, on p. 997. **Primary tumours** are described on p. 1122 : and **secondary malignant growth** of bronchial carcinoma in the choroid is illustrated in Figs. 351 and 733 on pp. 573 and 1146.

MENINGEAL ADHESIONS. In connection with the problem of the **prevention of adhesions** between the meninges and the subjacent surface of the brain after accidental or operative trauma, it has been found by Wilder Penfield and his co-workers [1] that these, and also the liability to post-traumatic and post-operative epilepsy, may be obviated by covering the exposed area of brain-surface with a sheet composed of the inner layer of the birth-membranes, to which they have given the name " amnioplastin." This can be prepared from the human afterbirth, sterilised, and then used as a protective covering between the brain and the replaced overlying membranes or other tissues. It is gradually absorbed, usually within a period of about thirty days, during which time the subjacent brain-tissue has the opportunity of healing and the subdural space of being re-formed, and adhesions thus prevented (*cf.* the absence of adhesions between the under surface of a chronic subdural hæmatoma and the subjacent brain, pp. 975–7).

THROMBOSIS OF THE CEREBRAL VENOUS SINUSES may be secondary to inflammation of the neighbouring dura-mater, which may itself be involved by the spread to it of disease from any of the cranial bones. The condition also results from trauma.

Thrombosis of a cerebral sinus may be **simple** or **septic.** It occurs as a complication or sequel of acute fevers, including puerperal infections, in wasting diseases ("**marantic**" thrombi), or in certain so-called "blood-diseases." It is found most frequently in the superior sagittal (or longitudinal) sinus, commencing at its anterior part and spreading backwards perhaps as far as the confluence of the sinuses and involving many of the tributary veins from the surface of the brain : or in the transverse and sigmoid sinuses : less frequently in the cavernous and intercavernous sinuses. In the last of these positions, however, the thrombosis is generally the result of pressure by tumours of the pituitary body or of the meninges, or of syphilitic disease of that part of the dura-mater which forms the walls of the sinuses. In the transverse (or lateral) sinuses, the thrombi are most commonly septic, arising by spread—directly through the bone or by way of the superior petrosal sinus—of infection from the middle ear, with or without necrosis of its bony roof. From the transverse and sigmoidal sinuses the infection may spread down the internal jugular vein. If the thrombosis is non-septic, it may lead to the production of venous congestion and rupture of small vessels on the surface of the brain, thus giving rise to hæmorrhages. If it is septic, the clot tends to undergo suppurative softening with resulting pyæmia (p. 981). Thrombosis of the straight sinus and of the great cerebral vein of Galen is of importance from the fact that by these channels blood is returned from the region of the basal ganglia and other parts of the interior of the brain.

Thrombosis of Cerebral Veins. Thrombosis in the superficial and other cerebral veins may occur as a so-called "primary" phenomenon in morbid conditions of the blood or of the circulation (pp. 165–6 and 500), and, like thrombosis of the veins of the pelvis or leg, is seen in some cases after child-birth, especially where there has been any puerperal or gastro-intestinal infection. " Secondary " thrombosis may follow any of the usual causes, such as infective phlebitis from middle-ear disease (p. 979), or compression or invasion of the veins by abscesses or tumours.

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[1] "A New Method of Preventing Adhesions: the Use of Amnioplastin after Craniotomy," by Yi-Cheng Chao, Storer Humphreys and Wilder Penfield (McGill University, Montreal), *Brit. Med. Jour.*, 1940, i, 517. This method may be used also for the prevention of adhesions in joints and around tendons.

MENINGEAL HÆMORRHAGE

Although the whole subject of **intracranial hæmorrhage** might conveniently be considered in one section, we shall discuss **meningeal hæmorrhage** at this point, and refer our readers to p. 1035 for the description of " cerebral hæmorrhage proper."

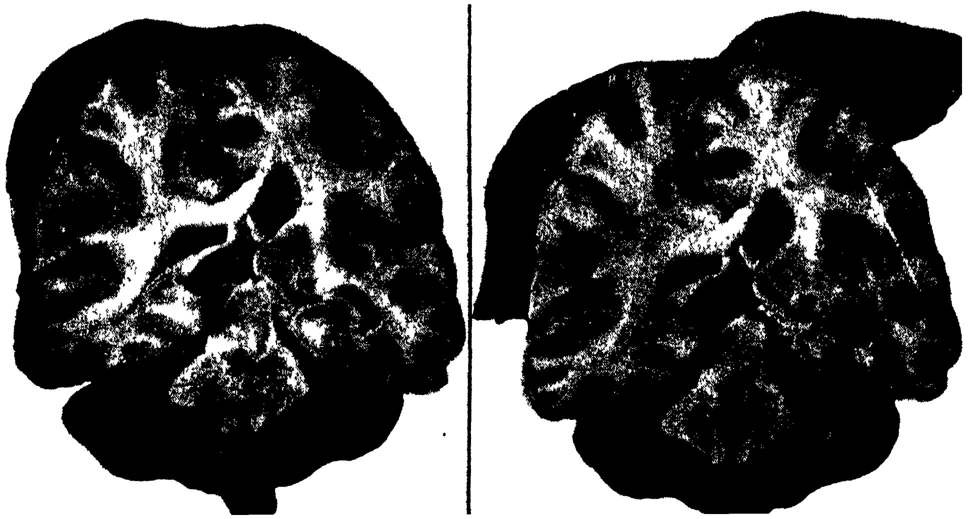
Hæmorrhages of varying size and importance into, on, or between any of the membranes of the brain may occur as a result of severe inflammation or in toxic diseases of various kinds, *e.g.*, in acute meningitis, septicæmia, typhoid, scurvy, and in coal-gas, arsenical and other forms of poisoning. In anthrax (p. 505), as pointed out by the late Professor W. S. Greenfield, " the brain may exhibit no conspicuous lesion, or there may be extensive hæmorrhages into its substance or in the membranes." Injuries of the skull or injuries of, and hæmorrhages spreading from, the brain itself may involve the membranes and give rise to extravasation of blood which may be **extradural, intradural, subdural, subarachnoid,** or a **combination of these.** Such hæmorrhages can be caused by fractures or by penetrating wounds of the skull : by simple contusions of the skull : and they may also occur without any external wound in concussion due to explosions. Similar hæmorrhages are sometimes found in tuberculous and meningococcal meningitis.

(1) **EPIDURAL** or **EXTRADURAL HÆMORRHAGE** between dura and bone is most frequently **traumatic** in origin, *e.g.*, from rupture of sinuses, veins or arteries, especially the **middle meningeal artery,** the anterior branch of which is liable to be damaged in the region of the pterion where the artery emerges from the deep groove or canal on the inner aspect of the antero-inferior angle of the parietal bone. A meningeal vessel may be torn by involvement in a fracture of the skull, or the dura can be detached from the bone without fracture by a severe blow on the head, the resulting hæmorrhage tending to be progressive and to spread by working its way between and separating the dura from the bone. A characteristic sequence in the symptoms after such accident is an immediate period of unconsciousness from concussion, and, as this passes off, a " lucid interval " of varying length, followed by relapse into unconsciousness from compression of the brain by the gradually increasing hæmorrhage. Hæmorrhage can also be caused even by a severe cough, especially if the vessels are already diseased and the blood-pressure high.

(2) **SUBDURAL HÆMORRHAGE: ACUTE and CHRONIC SUBDURAL HÆMATOMA.** Bleeding into the subdural space is caused most frequently by trauma. In its more **acute** forms, this variety of hæmorrhage is found in a considerable proportion of all cases of severe head-injury if these are examined, either operatively or *post mortem,* in from twenty-four hours up to several weeks

from the time of the accident. The development and persistence of headache, lethargy and mental disturbance after an accident of this nature should, therefore, indicate the necessity of keeping the possibility of the presence of meningeal hæmorrhage in mind.

Such bleeding may arise from torn cerebral veins or from lacerated brain-tissue. The blood collects between the dura and arachnoid, mixed, if the latter membrane has also been torn, with cerebrospinal fluid. Absorption from the subdural space is usually slight and gradual, and the clotting of the extravasated blood is often imperfect, perhaps because of admixture with cerebrospinal fluid.



(1) (2)

FIG. 588. *Subdural hæmatoma over right parietal region.*

(1) Large lentiform subdural hæmatoma causing distortion of subjacent hemisphere and its lateral ventricle. The actual hæmatoma was considerably larger, much fluid and semi-fluid blood having escaped during removal of brain at post-mortem.

(2) The same, showing hæmatoma slightly retracted to demonstrate new-formed membrane separating it from brain to which it was *not* adherent. Dura over opposite hemisphere also turned up to show other smaller, thin, patchy subdural hæmorrhages and old blood-pigment on its deep surface.

A study of these photographs will enable the reader to interpret the X-ray ventriculographic findings in such cases—lowering and displacement inwards of the lateral ventricle of the same side.

(The case was that of a man, aged sixty-eight years, with chronic nephritis and advanced arterial disease, especially of the cerebral arteries. Cerebrospinal fluid clear and colourless, *i.e.*, no blood had burst through into subarachnoid space : and the fluid otherwise normal for patient of this age. Wassermann reaction negative in both fluid and blood.)

The interior of the mass tends to remain liquid and become encysted, organisation spreading slowly inwards from the dura, but remaining incomplete if the mass is large (for further description see below).

Chronic subdural hæmatoma is commonest in males. It may at any age supervene upon the more acute variety, but it has been found most frequently in elderly patients suffering from some form of mental disease, or from epilepsy, syphilis (especially general paresis), or chronic alcoholism, in which vascular and other degenerations are common. In these patients, **trauma** is also undoubtedly the most important causal factor, although the injury may, from the nature of the case and the mental condition, have passed unnoticed. In newborn infants, subdural and other forms of meningeal hæmorrhage may be the result of head-injury during birth, but a predisposition to it is believed to be due largely to deficiency in prothrombin (p. 161) or of vitamin K (pp. 161, 442 and 587–8). In older infants, scurvy is often an important ætiological factor. Chronic subdural hæmatoma occurs most commonly over, and is usually confined to, the convexity of the brain, especially in the parietal region. The extravasated blood and the resulting hæmatoma vary in amount and extent from a small hæmorrhage up to a very considerable mass an inch or more in thickness and perhaps three or four inches in diameter (Fig. 588), producing, when viewed externally through the unopened dura, *e.g.*, through an exploratory trephine-opening in the skull, a dark bluish appearance. Unless the pia-arachnoid and its vessels have also been injured, blood is not found in the cerebrospinal fluid on lumbar puncture.

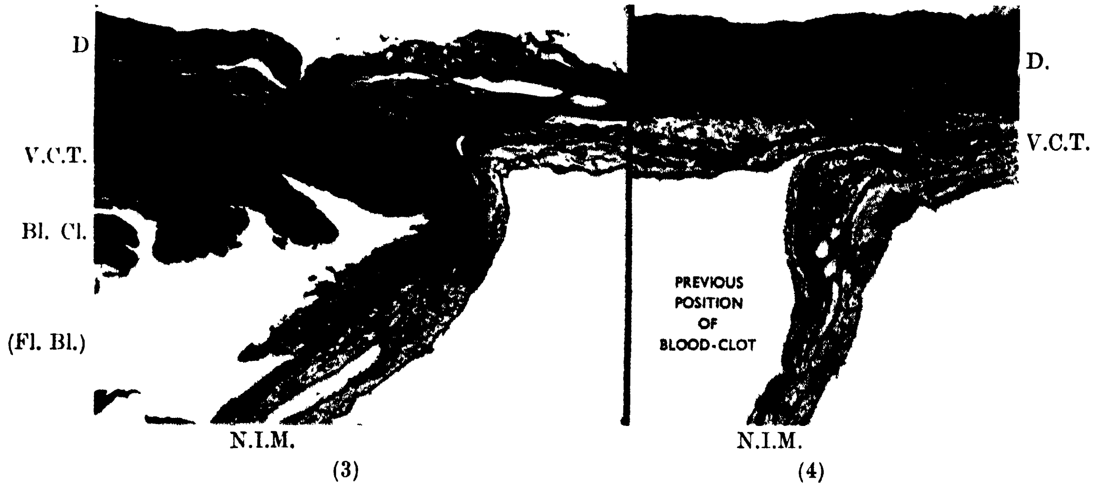


FIG. 589. *Subdural hæmatoma* (same case). Very low power views of sections of dura-mater (D) at periphery of hæmatoma, to illustrate formation of " *new membrane.*" × 20

The " new internal membrane " (N.I.M.) is seen arising from the deep surface of the dura (D). Much of the contained blood, still fluid, had escaped (Fl. Bl.). The part of the clot (Bl. Cl.) next and adherent to dura shows lamination and commencing organisation. Note thin-walled vascular spaces in dura parallel to plane of junction.

The vascular spaces in the inner or deep membrane (N.I.M.) were present in this case only towards its origin from the dura. The "new membrane" is, however, often more or less non-vascular.

On deep surface of dura, between it and blood-clot, is a layer of young vascular connective tissue (V.C.T.), from and by which the subjacent clot is gradually organised and absorbed—often imperfectly. A characteristic thin sheet of connective tissue (N.I.M.) is formed over the internal or deep surface of the clot, between it and the arachnoid, in contact with which it lies, but to which it usually does not become adherent.

(Worster-Drought and Carnegie Dickson's case. W.E.H.) Mallory's connective-tissue stain.

A characteristic phenomenon in connection with this lesion is the development of a **membrane** which spreads over the deeper surface of the hæmatoma by the proliferation of the subdural endothelial cells at the periphery of the mass.

This membrane is at first thin and delicate, transparent or semi-transparent, and often with a brownish or sometimes even greenish tint from the presence of blood-pigment or its derivatives. W. J. Gardner [1] (1932) suggests that the bulk of the contents of the hæmatoma may be increased by the osmotic absorption of liquid from the cerebrospinal fluid through this thin membrane, but this would imply some previous damage to the arachnoid in order to allow of access of the fluid through it into the subdural space and under-surface of the " new membrane." The clot gradually becomes densely adherent to the deep aspect of the dura, from which vessels and connective tissue pass into it—as in the vascularisation and organisation of a thrombus in a vein or artery (*see* pp. 51–2, and Figs. 27–8). There is, as a rule, little or no tendency for the clot to become adherent to the subjacent arachnoid and brain-surface, though this does occasionally take place if there has been injury of these structures, such adhesions being usually prevented by the formation of the endothelial membrane (for details of the structure of which see Figs. 588 and 589 ; and in this connection see also note on " Prevention of Meningeal Adhesions," p. 973). In some 30 per cent. of the cases, subdural hæmatomas are present on **both** right and left sides. The lesions may be **multiple,** or may **recur** several times over the same area, then giving rise to laminated clots of different ages, mixed, perhaps, with recent semi-fluid or fluid blood or separated blood-serum, which, if not absorbed, may become encysted. Considerable, though often incomplete, absorption may ultimately take place, and a thickened and sometimes laminated and pigmented fibrous scar, coalescing with the inner or deep surface of the dura, persists, perhaps enclosing some remains of the original blood-clot. The formation of a similar new or false membrane has been described by Dorothy Russell and Hugh Cairns (1934) over the deep surface of new growths infiltrating the dura.

The chronic forms of organised or partially organised subdural hæmatoma have been called " pachymeningitis hæmorrhagica interna chronica," and an analogous lesion is found, though more rarely, in the spinal canal (p. 991). As the lesion is *not* inflammatory in nature, but, as explained above, is a sequel of hæmorrhage, the term "meningitis" is inappropriate.

(3) **SUBARACHNOID HÆMORRHAGES** arise from any of the causes already enumerated, and may be small and petechial or larger and more diffuse, in the latter instance extending, it may be, over a considerable surface of the brain. On lumbar puncture, blood is found in the cerebrospinal fluid for the first few hours up to two or three days, in the form of fresh non-hæmolysed red corpuscles. Later, as these undergo hæmolysis, the fluid becomes of a yellowish or more rarely of a slightly reddish tint, the colour as a rule disappearing in two or three weeks, unless there has been further bleeding (*see also under* " Xanthochromia," p. 963).

Subarachnoid hæmorrhages may follow thrombosis of the superior sagittal (longitudinal) sinus—the larger surface cerebral veins opening into it becoming engorged and sometimes thrombosed, and their smaller tributaries dilated and undergoing rupture.

One of the most important causes of subarachnoid hæmorrhage is

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[1] *Archives of Neurology and Psychiatry,* 1932, **27,** 847.

leakage—often recurring over a considerable period even of years—**from, or rupture of, an aneurysm** on one of the cerebral arteries, *e.g.*, the circulus arteriosus (circle of Willis) or one of its branches (p. 1042 *et seq*).

An *intra*cerebral hæmorrhage may burst into one of the lateral ventricles. The blood then makes its way through the interventricular foramina of Monro into the third, and opposite lateral, ventricles, and down the aqueduct of Sylvius to the fourth ventricle, whence it escapes into the subarachnoid space and cisterns. It may then gradually extend between the arachnoid and the pia until it comes to cover both the under and the upper surfaces of the cerebellum and perhaps also may spread for a varying distance over the surface of the cerebrum, along the lines of the lateral fissures of Sylvius, or pass anteriorly into the longitudinal fissure over the upper surface of the corpus callosum, and into the sulci on the mesial surface of the hemispheres. It may also extend down the spinal theca and be detected on lumbar puncture.

Blood in any appreciable quantity **mixed with the cerebrospinal fluid** in the subarachnoid space acts as **an irritant,** and may produce clinical signs and symptoms simulating those of meningitis. These may include a rise of the cerebrospinal pressure, due in large part to the action of the extravasated hæmoglobin and the presence of the serum-proteins, bringing about increased osmosis of fluid from the blood (p. 963), rather than, as has sometimes been thought, from the mechanical blocking of the arachnoidal villi by the red corpuscles and consequent interference with the re-absorption of the fluid through them into the blood. It has, indeed, been found experimentally that the injection of washed and non-hæmolysed red corpuscles does *not* produce these results, whereas the introduction of a sufficient quantity of blood-serum or blood-plasma leads to a distinct rise in pressure.

Intracerebral hæmorrhage or **cerebral hæmorrhage proper** is discussed on p. 1035 *et seq.*

INFLAMMATION OF THE MEMBRANES—MENINGITIS

PACHYMENINGITIS or INFLAMMATION OF THE DURA-MATER is usually secondary to injury, or to disease, of the accessory para-nasal or other air-sinuses, the ear, or the bones of the skull. Thus it may be caused by trauma : by tumours growing from the bones of the skull or invading the cranial cavity through the bones or by passage along foramina : by gummata of the skull (Fig. 602, p. 1004) as well as of the dura itself : and by suppuration extending from the middle ear either directly through the bone or by way of the transverse sinus. Caries or necrosis of bone, the result of tuberculosis or of syphilis, may also give rise to inflammation ; and syphilitic meningitis sometimes occurs without the formation of gummata and without necrosis of bone.

Effects of Septic Pachymeningitis. When the outer part of the dura alone is diseased, the membrane is swollen and dark-red or greenish in colour, and may become separated from the bone by an extradural collection of pus. On its inner surface, there may be a thin layer of greenish-yellow lymph, tending to spread rapidly and extensively until the pia-arachnoid is involved, with purulent effusion in the subdural and subarachnoid spaces. If the patient survives long enough, granulation-tissue develops and adhesions form between the pia-arachnoid and the dura.

LEPTOMENINGITIS or INFLAMMATION OF THE PIA-ARACHNOID. As leptomeningitis is much commoner than inflammation of the dura, the unqualified term "meningitis," as commonly employed, is often used to denote inflammatory changes in the pia-arachnoid.

Ætiology. In leptomeningitis, the commonest route of infection is the blood-stream. Lymphatic channels and the lymphatic spaces in the areolar tissue of the face and scalp are also potential pathways of infection, as are thrombosed veins communicating with the interior of the skull, *e.g.*, through the diploë of the cranial bones. Direct spread by continuity from the middle ear or from the nasal cavity and its accessory sinuses is not uncommon ; and leptomeningitis may be caused also by direct spread from inflammatory foci in the dura-mater or from the brain itself. Other important routes are the prolongations of the subarachnoid space around certain of the cranial nerves, more particularly the olfactory, optic and auditory. Thus an ophthalmitis of one eye may spread backwards along the optic nerve-sheath and come to involve, not only the opposite eye, but also the meninges. Surgical interference with a tuberculous lesion of the upper region of the nasal passages is liable to be followed by tuberculous meningitis ; and in this connection may be mentioned the fact that certain viral diseases (pp. 97–8, and p. 105 *et seq.*) spread to the central nervous system by way of the nerves, probably along the interior of the nerve-fibrils themselves, *e.g.*, from the nose, naso-pharynx or elsewhere.

FIG. 590. Polymorphonuclear exudate in a case of acute purulent meningitis due to *Streptococcus mucosus* a not uncommon organism of middle-ear and sinus-infection. Leishman's stain. × 1,250.

Meningitis may arise, either primarily or secondarily, in the acute infective diseases, *e.g.*, in influenza and pneumonia, and as a complication or sequel of measles, whooping-cough, mumps, or during an attack of acute rheumatism, in nephritis, or in the course of any form of tuberculosis ; and in these various diseases the meningitis may be caused by the specific organism itself—whether bacterium or virus—or by some organism of secondary infection. The commoner causal organisms of meningitis are streptococci, pneumococci, meningococci, staphylococci and the tubercle bacillus. Less frequently, meningitis occurs as a complication in typhoid and paratyphoid fevers and anthrax. In some instances, organisms of the hæmophilus, leptothrix and streptothrix groups, and torula- (blastomyces, cryptococcus, etc.) and monilia-forms have been isolated. In others, no bacteria have been found, some of these being due to viral infections (pp. 116–17 *et passim:* and 1000).

"Meningeal irritation," toxic in origin and independent of the local presence of organisms, but giving rise to symptoms closely simulating those of meningitis, is not uncommon in apical pneumonia in children and in certain other acute infective diseases, and is then described clinically as "**Meningismus.**"

Pathological Anatomy of Meningitis. Excluding for the present the specific infections due to meningococci (p. 981), the tubercle bacillus (p. 992), the spirochæte of syphilis (p. 1002), and certain viruses (p. 105 *et seq.*), which are described under separate headings, **leptomeningitis** in its earliest stage manifests as a rosy-red coloration of the pia-arachnoid, due to distension of the surface vessels ; and there may be petechial or sometimes larger hæmorrhages.

In pyogenic infections of the pia-arachnoid, a turbid inflammatory exudate, generally bilateral and symmetrical, develops, spreading especially along the lines of the vessels, filling up the sulci and obscuring the convolutions, and, later, showing as a thick semi-translucent yellowish-white gelatinous layer over the surface of the brain. The exudate may become more opaque and definitely purulent, filling the meshes of the subarachnoid space with pus.

The **cerebrospinal fluid** is under increased pressure and is increased in amount, turbid, with, at first, a characteristic "ground-glass" opacity. Later, it becomes thick and purulent or fibrino-purulent in character. On standing after withdrawal, the cells sink to the bottom of the tube and the supernatant fluid has a dirty-yellowish discoloration or a varying degree of brownish-red blood-staining. Coagulable protein, both albumin and globulin, including fibrinogen, is greatly increased in amount, the presence of free complement may be demonstrated, chlorides and sugar are diminished and the latter may entirely disappear (see also pp. 963–4). The causal organisms, if bacterial (as is practically always the case in purulent meningitis), may usually be demonstrated in the fluid microscopically and by culture. In the case of certain of the viral infections, which are never frankly "suppurative," inoculation into a susceptible animal (if such be available) and other special methods are required for full identification.

The cerebral cortex shows inflammatory hyperæmia, which sometimes spreads inwards along the vessels for a varying distance from the surface, constituting an encephalitis or inflammation of the brain-substance ; and, occasionally, smaller or larger patches of softening or small abscesses are found. Microscopically, these inflamed and softened patches show dilatation of the minute vessels, inflammatory œdema and degenerative changes in nerve-cells.

The meningitis may in varying degree be localised or diffuse, and attempts have been made to classify the various forms or types according to their situation and by the character of the exudate. Thus it is claimed that the exudate in pneumococcal infection is thick, viscid and greenish-yellow in tint ; whilst that due to streptococci and staphylococci is more fluid, serous or sero-purulent and paler in colour. Again, in those cases which are secondary to disease of the middle ear, the pus may be most abundant over the adjacent temporal (temporo-sphenoidal) lobe ; or over the medulla, pons, etc., where the inflammatory process has spread upwards from the spinal cord ; whilst in those in which the infection has been carried by the blood (and if the surface of the brain has not been reached from the choroids by way of the ventricular system) the exudate may be most pronounced over the vertex, as in some pneumococcal cases—presumably by the lodgment of the organisms or minute emboli containing them in the small terminal cerebral or meningeal vessels in that position. In staphylococcal and streptococcal infections in which pyæmia supervenes (pp. 973–4), focal suppurative lesions, *i.e.*, embolic pyæmic abscesses, may occur in any part of the brain, not infrequently in the region of the vertex, and from these foci of suppuration there usually is extension to the meninges. Though these differences in the naked-eye appearance and site of the exudate are distinguishable in certain instances and may be useful as rough guides in post-mortem diagnosis, too much reliance must not be placed on them. As will be noted more particularly in the following section, in cerebrospinal fever and perhaps also in many cases of tuberculous meningitis, a " basal " or " post-basal " distribution of the exudate may indicate that the surface infection of the meninges is due to, and has followed, a spread from the circulating blood through the choroid plexuses to the ventricles in the interior of the brain (p. 983).

As in the instance of meningococcal infections (*see* footnote to p. 985), so also in strepto-, pneumo-, staphylo-coccal, and other forms of bacterial meningitis, the **prognosis,** since the introduction of **chemotherapy** (*e.g.*, with sulphapyridine or one of its soluble forms such as sodium sulphapyridine—" M. & B. soluble 693 " : or sulphathiazole—" M. & B. 760 ") is now very much more favourable than previously, when the great majority of such infections were practically always fatal.

MENINGOCOCCAL MENINGITIS (**CEREBROSPINAL or SPOTTED FEVER**) is a general infectious or infective disease with a tendency to localisation in the choroid plexuses, ventricles and leptomeninges of the brain. It occurs in epidemics, chiefly in late winter and spring, reaching its maximum incidence in March or April ; but sporadic cases are not uncommon. Young persons are most liable to be attacked, and the infection is often associated with bad hygienic conditions, especially overcrowding, *e.g.*, in barracks, camps, schools and other institutions.

The micro-organism concerned (of which **two chief types** or **groups, I** and **II,** are now recognised) is the *Neisseria intracellularis, Neisseria meningitidis* or meningococcus, described originally in 1887 by Weichselbaum as the " *Diplococcus intracellularis meningitidis.*" The usually milder or less pathogenic **type-II** is the commoner variety found in the nasopharynx in many apparently healthy people. Although it is mostly in infants or in individuals with low powers of resistance that the latter type of meningococcus is a serious cause of meningitis, it has, however, sometimes been isolated from severe, and even rapidly fatal, infections in previously apparently healthy persons. The more important and more pathogenic **type-I** occurs as the predominant variety of meningococcus in persons who, particularly during epidemics, have been in close contact with patients suffering from cerebrospinal fever : and, especially during the first week or ten days of the illness, in patients who are suffering from the disease itself, among whom a certain proportion are or become " carriers." In these carrier-cases it is often difficult to get rid of the organism, even when the nasopharynx is apparently " normal," but more especially if there are obvious pathological changes present and if the meningococcus has obtained entrance to the ethmoidal, sphenoidal or other para-nasal sinuses. Much effort, usually, it must be confessed, with comparatively little success, was, during the War of 1914-18, devoted to attempts at the sterilisation of the nasopharynx of carriers and contacts, but this is now considered scarcely necessary,[1] except in the case of persons suspected of being the source of epidemics in, say, institutions such as schools, and then only if the more dangerous **type-I** meningococcus is identified as being present.

" For every case of meningococcus infection which results in cerebro-spinal fever, there are many more which do not. . . . the great majority of infections are derived from persons who, for the time being, are unrecognised carriers of the meningococcus " and " it must be assumed that the great majority of patients contract their infection from carriers." From lack of susceptible laboratory animals, virulence-tests cannot ordinarily be applied.[2]

In 1915, Sir Joseph Arkwright [3] came to the conclusion that, from the epidemiological point of view, " the carriers constitute the mass of the epidemic, and those who subsequently develop meningitis are only a small accidental minority "—*i.e.*, an " epiphenomenon," as it has been termed—of the more generalised epidemic of catarrh. He did not at that time consider himself in a position to determine whether the attack on the meninges was due to lessened resistance, local or general, on the part of the patient, or to increased virulence on the part of the micro-organism.[3] Maclean and Bevan [4] suggest that the rapid passage of the meningococcus, along with other catarrhal organisms—chiefly by " droplet " infection—from patient to patient during epidemics of naso-pharyngeal catarrh, is probably one of the main factors in the production of this rise in virulence. In " A Study of the Naso-pharyngeal Bacterial Flora of Different Groups of Persons observed in London and South-East England during the years 1930 to 1937," [5] it is stated that, of adults in normal health living in urban communities in a temperate zone, some 5 to 20 *per cent.* were found to harbour the meningococcus ; 20 to 40 *per cent.* the pneumococcus ; 5 to 15 *per cent.* a hæmolytic streptococcus ; and 40 to 80 *per cent.* Pfeiffer's bacillus. It is probable that some three-quarters of the members of this " sample population " had, at one time or another within a period of six years, harboured the meningococcus and a hæmolytic streptococcus (*loc. cit.*, p. 128).

FIG. 591. Exudate in epidemic cerebrospinal meningitis, showing breaking-down pus-cells crowded with meningococci. (Leishman's stain. × 1,250.)

In meningitic cases, the *Neisseria intracellularis*, as its name implies, is commonly (but not invariably) intracellular; and, particularly in some of the more virulent and acute forms of the infection, a considerable proportion of the cocci may remain extracellular, or may become freed by the death and disintegration of many of the pus-cells which had contained them. On lumbar puncture, the organism is usually demonstrable in the cerebrospinal fluid, in which, in individual cases, it may be abundant or scanty, but sometimes, even in undoubted cases of the disease, it may not be detected. This is especially the case during the early period of invasion, or in the later stages if the condition is improving. Carnegie Dickson,[1] working at Fulham Military Hospital, the special centre for the treatment of cerebrospinal fever in the London district during the War of 1914–18, found the organisms practically uniformly and often in large numbers **in the intraventricular fluid** in a series of 144 consecutive post-mortems, as well as in the fluid obtained by ventricular puncture from certain of these cases during life, and also from a number of non-fatal cases.

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[1] *Memorandum on Cerebro-spinal Fever*, Ministry of Health Memo. 234/Med., H.M. Stationery Office, March, 1940.

[2] *Ministry of Health Report*, No. 65, on " A Review of Certain Aspects of the Control of Cerebro-Spinal Fever." H.M. Stationery Office, London, 1931, pp. 11–12.

[3] J. A. Arkwright " Cerebro-Spinal Meningitis. The Interpretation of Epidemiological Observations in the Light of Bacteriological Knowledge," *Brit. Med. Jour.*, 1915, **i**, 494.

[4] I. H. Maclean, and C. E. Bevan, " Observations on an Epidemic of Cerebrospinal Meningitis in Cyprus and the Record of a Prophylactic Experiment," *Proc. Roy. Soc. Med.*, London, 1939, **32**, 1551.

[5] By Edith Straker, A. Bradford Hill and R. Lovell (London School of Hygiene and Tropical Medicine), Ministry of Health Report No. **90**, 1939. (See Leading Article, "The Nasopharyngeal Flora in Health," in *Brit. Med. Jour.*, 1939, **ii**, pp. 1094–5.)

Early in the course of the disease, the meningococcus is obtainable culturally **from the peripheral blood,** and the disease may thus be regarded as primarily a **septicæmia.** In some intensely acute or fulminant cases, death within a few hours of the onset of symptoms ensues during this septicæmic phase, and before any definite local naked-eye inflammatory changes other than perhaps some acute congestion have had time to become evident in the brain, although in such cases the organism itself may be demonstrable in the ventricles and meninges. Though there are those who still believe that this specific localisation occurs first in the meninges, Carnegie Dickson, whilst not denying the possibility of this in individual cases, is, from the detailed investigation of the foregoing series of cases, of opinion that in all of these the portal of entry of the meningococci from the circulating blood had been **by way of the choroid plexuses**, from which the organisms had then spread into and involved the ventricular system, producing there a meningococcal **endoventriculitis.** The infection can then readily pass through the walls of this system where these are thinnest (Fig. 573, p. 957) and thus reach the surface of the brain and involve the meninges at these localities, *i.e.*: (1) through the distended and thinned floor of the third ventricle and infundibulum to the interpeduncular cistern around the pituitary stalk, from optic commissure in front to crura and pons posteriorly: (2) backwards through the great transverse fissure to the adjoining central portion of the upper surface of the cerebellum: and (3) through the ependymo-pial roof of the fourth ventricle and its foramina to the medulla and under aspect of the cerebellum.[2] From these particular areas it then spreads and coalesces to give the typical " basal " or " post-basal " distribution, and it also extends down the cord, and to a varying degree in all directions over the rest of the brain until the whole surface may ultimately become involved. The exudate appears to be perhaps least liable to spread forwards over the cribriform plates of the ethmoid round the olfactory tracts and bulbs, a point which seems to militate against the view put forward by some writers that the infection first spreads to the brain through the roof of the nose and cribriform plate. On the surface of the brain, the pia-arachnoid at first shows hyperæmia and serous exudation, with the presence microscopically of a few leucocytes and red corpuscles; but later, in patients who have survived longer, the exudate becomes definitely purulent and the pathological picture then resembles that seen in pneumococcal and other forms of purulent leptomeningitis.

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[1] "Cerebrospinal Meningitis: A Preliminary Note on Certain Pathological Findings and Their Bearing on Treatment," by Carnegie Dickson, *British Medical Journal*, 1917, **i**, 454.

[2] Additional evidence in support of the accuracy of these observations is given by the findings in a case described on p. 1054, viz.: that a meningitis with the posterior basal distribution characteristic of meningococcal infection can be brought about by other organisms if these are introduced into the ventricular system (Figs. 643–4 and 5). This was a case of very chronic multiple cerebral abscesses produced by a staphylococcal infection spreading from the left frontal sinus. The infection, completely sealed off from the meningeal surface of the rest of the brain by the chronic adhesions, slowly burrowed its way towards and into the anterior horns of the lateral ventricles. When these were reached, an acute endoventriculitis was produced, rapidly followed by **an acute posterior basal** staphylococcal meningitis from which the patient died in a few days. The acute terminal infection of the surface of the brain with *Staphylococcus aureus* had taken place exactly at the various points described above as characteristic of the meningococcal spread from the ventricular system to the meninges.

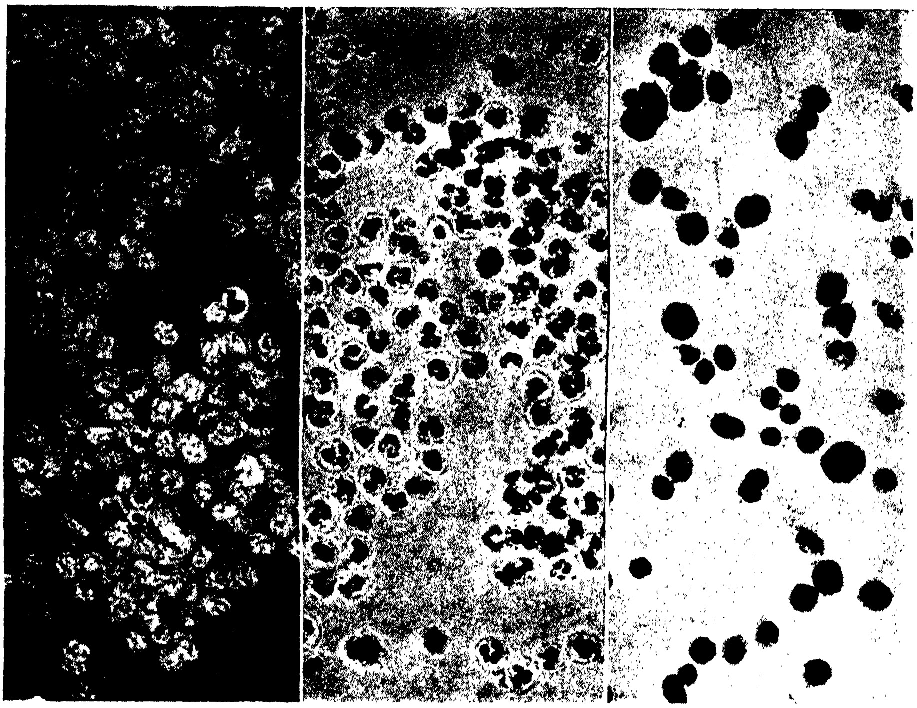
Within the ventricular system itself, the accumulation of infective exudate mixed with cerebrospinal fluid gives rise to a general **ependymitis** or **endoventriculitis,** with a varying amount of **periventricular softening,** *i.e.*, an **encephalitis,** which appears to be one of the most important factors leading to a fatal issue, especially where it involves the structures in the floor of the fourth ventricle. Such inflammatory softening is not infrequently accompanied by **hæmorrhages** into the brain-substance, perhaps small and scattered, but occasionally of considerable size, and sometimes rupturing into the ventricles; and the blood or deeply blood-stained fluid and exudate may then find its way downwards into the spinal theca, where it may be detected on lumbar puncture.

Varying degrees of **inflammatory hydrocephalus** are thus produced, and the accumulation of fluid is also in part brought about by interference with its free passage through the cerebral aqueduct (the walls of which may be swollen) and by the blocking of the various openings which normally establish communication between the ventricular system and the general subarachnoid space.

Such acute inflammatory hydrocephalus has to be distinguished from the mechanical dilatation of the ventricles which supervenes later in the course of the disease in cases in which the meningitis has itself cleared up or become " chronic," but in which the foramina in the ependymo-pial roof of the fourth ventricle have become permanently closed by fibrous-tissue adhesions. An internal **retention-hydrocephalus** (p. 966) is thus produced and, if not relieved, may ultimately cause death.

Another factor which aids mechanically in the production of hydrocephalus is the formation of a "pressure-cone" (p. 967), leading to obstruction by the compression of the foramina in the roof of the fourth ventricle and preventing the egress of fluid even when these foramina are not actually sealed by exudate. When the presence of this is suspected clinically, it may be safer to perform ventricular rather than lumbar puncture, as the latter may aggravate the impaction of the pressure-cone into the foramen magnum.

The Cerebrospinal Fluid in Meningococcal Meningitis. In the earliest phase of the disease, when cerebral symptoms are only just commencing, the **lumbar-puncture fluid** may to the naked eye still be comparatively, or even quite, clear and colourless—a point which should not be forgotten in the interpretation of such a finding in an early first-puncture fluid from a suspicious case (see below); but within a few hours the typical characteristics of an acute purulent infection



(1) (1A) (2)

FIG. 592. *Meningococcal meningitis* in a man aged twenty-three : *fresh-wet toluidin-blue preparations of typical early and late exudates :*

(1) *First lumbar-puncture fluid* on *second day of illness*, before commencement of treatment. Film made and photographed immediately : exudate predominantly polymorphonuclear, the unstained cells being still alive, and the stained cells dying or dead. The background consists of the fluid still containing excess of stain.

(1A) *The same preparation* photographed next day. The cells are now dead, and their nuclei have taken up the available remaining toluidin-blue stain.

(2) *Fourth lumbar-puncture fluid* on *seventh day of illness*. The patient, under treatment with M. & B's. " soluseptasine," was now convalescent, and the exudate almost entirely mononuclear. For details of the transition from a polymorphonuclear exudate, to one consisting of larger, and then of smaller, endothelial, and finally of small lymphocyte-like cells, see Figs. 593–4 : and 578 (p. 961). (W.E.H. case.) × 400.

(p. 958 *et seq.*) become established, the predominating cells being polymorphonuclear leucocytes in increasing numbers, many of them, in a typical example, containing meningococci in their cytoplasm (Figs. 591 and 594). Where improvement takes place, especially under treatment by suitable chemotherapy,[1] (or, if

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[1] The drugs which have now revolutionised the treatment and radically improved the prognosis in cerebrospinal fever are derivatives of the sulphonamide series : (i) M. & B. 137, or Soluseptasine, (ii) M. & B. 693, or Sulphapyridine, (iii) Sulphanilamide (trade synonyms Sulphonamide P., Streptocide, Prontosil album) : and (iv) the still more recent and efficacious M. & B. 760, or sulphathiazole (p. 981). Group-I and Group-II Meningococci appear to be equally susceptible to these drugs. . . . Before the introduction of soluseptasine, sulphapyridine was considered to be the drug of first choice . . . because it is not only as effective in the treatment of meningococcal and streptococcal infections . . . but is unique in its action in pneumococcal infections. . . . *The two essentials of this method of treatment are early administration and adequate dosage. Directly a clinical diagnosis is made, chemotherapy should be commenced without waiting for bacteriological confirmation.* (Modified from Ministry of Health Memo., 234/Med., 1940, p. 6.) In R. W. Cushing's " Analysis of 124 Cases of Cerebrospinal Fever " in the *British Medical Journal*, 1940, ii, 439, soluseptasine (M. & B. 137) was found to be more efficacious and less toxic than the other two preparations, and, by its use in this series of 124 (plus 11 subsequent) cases, the mortality was reduced to just under 3 per cent. Still further improvements in this line of treatment are probable in the immediate future.

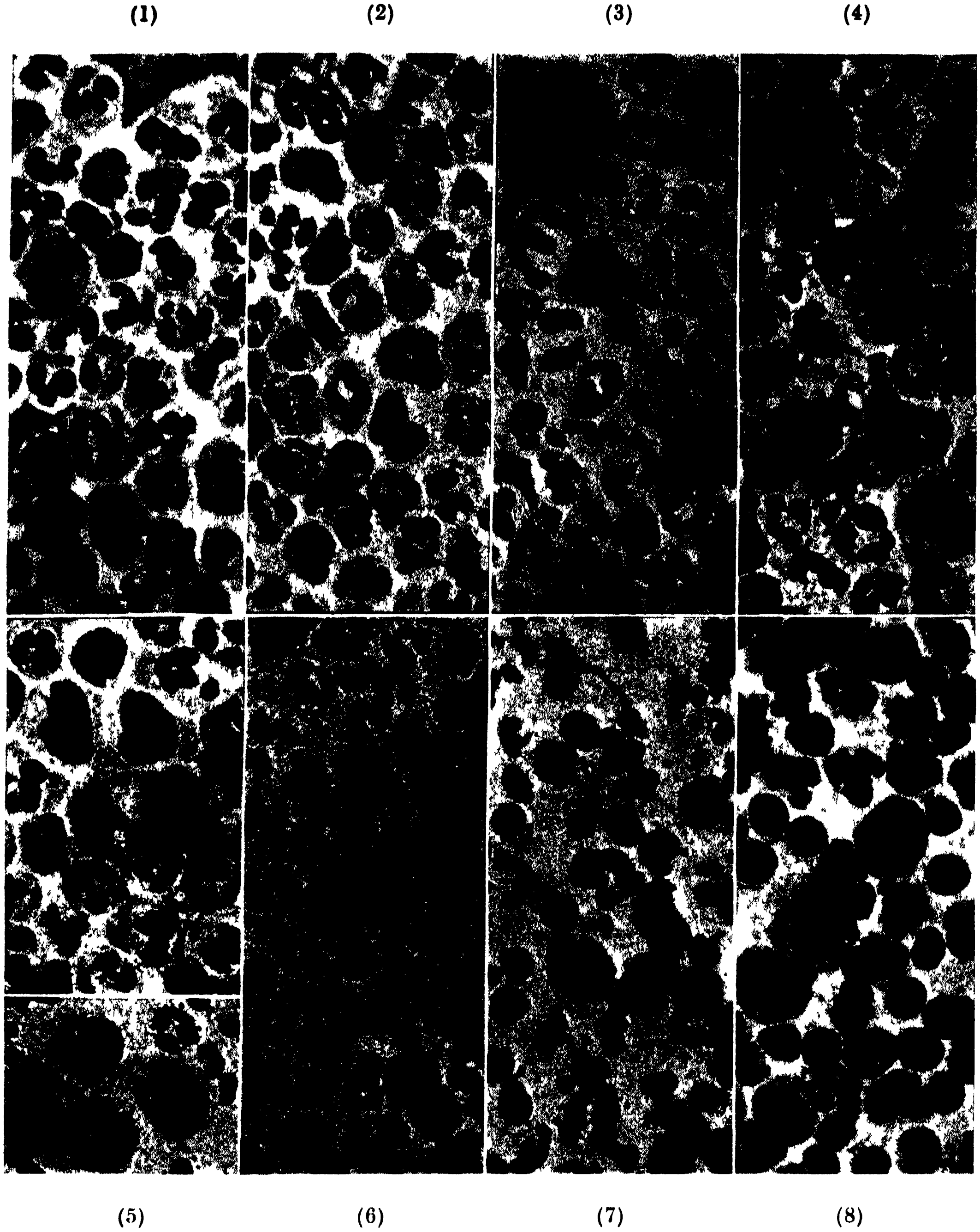
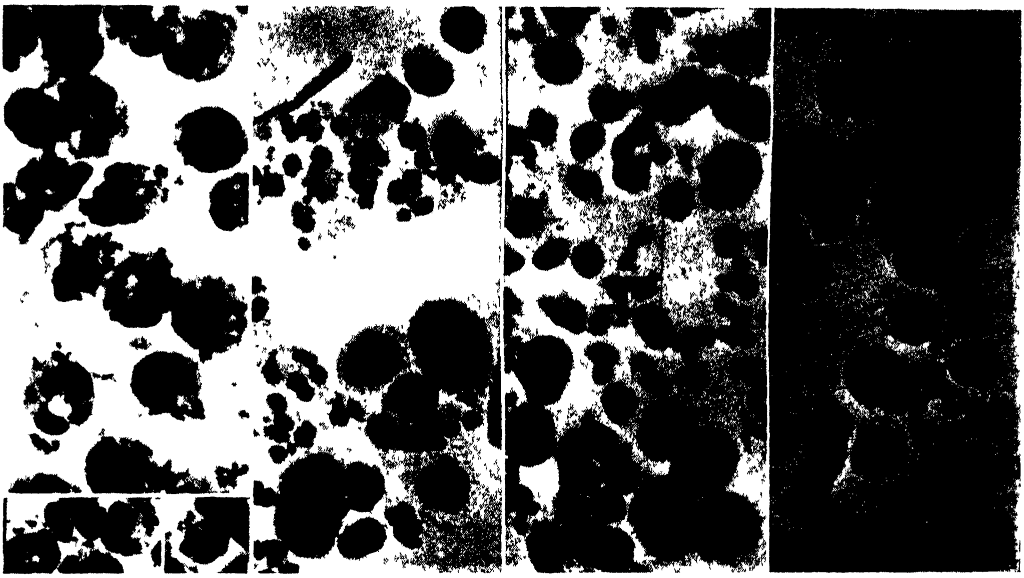


FIG. 593. *Acute meningococcal meningitis, from the second to the seventh days of illness,* in man aged twenty three (from whom the illustrations in Fig. 592 were also taken)—to illustrate the details of *the transition from a polymorphonuclear to a mononuclear type of exudate.* As the polymorphs diminish in numbers, not only separate single mononuclear cells, but also small sheets or flakes of proliferated endothelium, often appear, *e.g.*, as in (3), (4) and (5)—at first mostly *large* cells, but becoming, on the whole, *progressively smaller,* until finally only a few "*small lymphocytes*" are left, as in (4) of Fig. 578 on p. 961. That these smaller cells are the product of the mitotic division of preceding slightly larger cells can be observed from the study of this or any similar series of fresh-wet films (*cf.* Figs. 578 and 594). (W.E.H. case.) Fresh wet toluidin-blue preparations. × 1,000.

the case is acute or fulminant, chemotherapy *combined with* the administration of anti-meningococcal serum), the polymorphs gradually diminish in number and become replaced by larger and then by progressively smaller mononuclear cells, the micro-organisms disappear, and the condition may clear up entirely (Figs. 591 to 594). In certain cases in which these changes occur in the lumbar-puncture fluid, but in which there is not a corresponding clinical improvement, the explanation may be that, as described above, the foramina in the ependymo-pial roof of the fourth ventricle may have become obliterated by fibrous-tissue adhesions and a retention-hydrocephalus is supervening. In meningitic cases which do not run a favourable course, however, the polymorphs and perhaps also the meningococci, often along with varying proportions of red corpuscles, persist and increase in number, until a fatal termination is reached.



(1) (2) (3) (4)

FIG. 594. *Acute meningococcal meningitis* in a girl aged ten years, treated with M. & B's. "soluseptasine"—recovery.

(1) *First lumbar-puncture fluid* on *second day of illness*: numerous meningococci present, mostly intracellular.

(2) *Third lumbar-puncture fluid* on *fourth day of illness*: large endothelial cells (*one of them in mitosis*): smaller endothelial cells formed from these: and small "lymphocyte-like cells": polymorphs degenerated and in diminishing numbers.

(3) *Fourth lumbar-puncture fluid* on *fifth day of illness*: note all transitions from larger to smaller endothelial cells. One of the latter (marked with arrow) has just undergone mitotic division, and near it are intermediate and small endothelial cells and "small lymphocyte-like cells."

(4) *Fifth lumbar-puncture fluid* on *sixth day of illness*: small endothelial and lymphocyte-like cells now predominate. At top of photograph a division has just occurred, with the formation of cells indistinguishable from small lymphocytes. (W.E.H. case.) Fresh-wet toluidin-blue preparations. × 1,000.

As already indicated, considerable differences may be found in the characters of the ventricular, cisternal and lumbar-puncture fluids obtained simultaneously from the same patient, these differences depending, amongst other factors, upon the stage of the disease and the severity and distribution of the inflammatory process. Very early in the infection, whilst the lumbar fluid obtained by the first puncture may, as noted above, still be clear and colourless, and contain perhaps few or even no pus-cells, and whilst its chloride- and sugar-content may still remain normal, the **ventricular** fluid may already show pronounced evidence of inflammation and contain large numbers of meningococci, which may in some cases be out of all proportion to the cell-content. As the inflammatory phenomena become established and the exudate spreads over the base and down into the spinal theca, the lumbar-puncture cell-content may often, but does not in every case, come to exceed that of the ventricular fluid, though sometimes the number of cells found in the **cisternal** fluid may be greater than either. Most observers who have investigated the point have found that, at all stages of the disease, the organisms themselves are more numerous in ventricular than in lumbar fluids—in serious cases so numerous, indeed, as almost to resemble a " cultural " growth. In the fluids from both sources, a protein-increase to 100 mgr. or up to even 2,000 mgr. (2 grammes) or more per 100 c.cm. may be found, accompanied by a diminution of chlorides and sugar. The sugar may, particularly in the lumbar fluid, even entirely disappear. This diminution, especially early in the disease, is usually less pronounced in the ventricular than in the lumbar fluid, because, as the fluid percolates downwards, a progressive glycolysis is brought about by the action of the inflammatory cell-ferments and of the meningococci.

During epidemics of cerebrospinal fever in the past, it has occasionally happened that cases of tuberculous meningitis or of neurosyphilis have received an intrathecal injection of **antimeningococcal serum.** This in those patients produced a marked **polymorphonuclear pleocytosis** which entirely masked the original condition in the cerebrospinal fluid.[1] The findings simulated those in an acute purulent meningitis indistinguishable from a meningococcal infection itself, except for the fact that the typical organism was absent. If the possibility of the occurrence of these misleading appearances is borne in mind, the diagnosis of such otherwise puzzling cases may be cleared up by the finding of the tubercle bacillus or by a positive Wassermann reaction. Since the introduction of the chemotherapeutic treatment of meningococcal meningitis, however, these phenomena are less likely to be encountered. (*See also* pp. 985 and 994–5.)

Complications and Sequelæ. Herpes is common on the lips, and a hæmorrhagic petechial rash is frequently present. Subcutaneous hæmorrhages may be few in number, or in other cases widespread and numerous, and sometimes of large size ; and it is because of the occurrence of this hæmorrhagic rash that the disease is popularly known as "spotted fever." Some observers have described the cultivation of meningococci from these cutaneous hæmorrhages. Emaciation, especially in children, and if the condition becomes chronic, is often extreme, and bed-sores may develop. In the blood, a polymorphonuclear leucocytosis of 20,000 to 40,000 per c.mm. may be present. The occasional occurrence of arthritis, *e.g.*, of the knee-joint, with meningococci in the exudate, has been recorded; but transitory arthritic symptoms were by no means uncommon in serum-treated cases and were then probably an anaphylactic phenomenon due to the foreign-protein content of therapeutic sera rather than a true meningococcal arthritis. Occasional instances of meningococcal endocarditis and pericarditis, and also parotitis, have been recorded.

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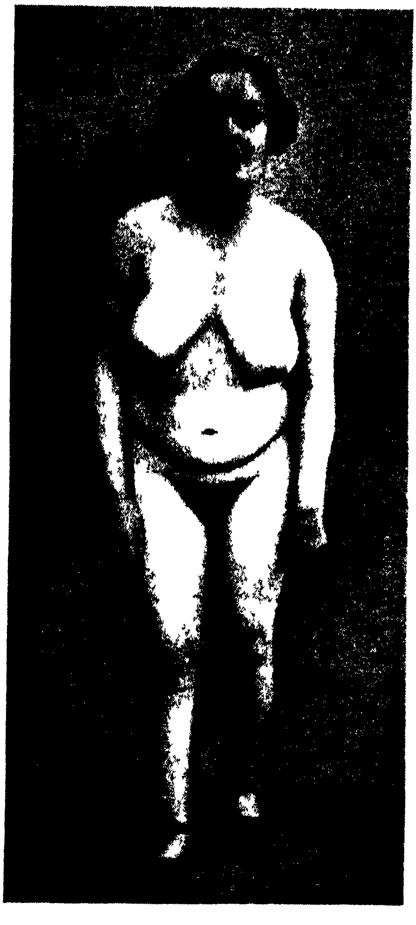
[1] Carnegie Dickson, *loc. cit.* (*see* first footnote on p. 983).

Pneumonia and its accompanying pleurisy, occurring as a complication of this as of many other acute fevers, is perhaps due most commonly to secondary infection with, say, pneumococci or streptococci, though some observers have described the occurrence of meningococci along with these. Pyelitis, thrombophlebitis and gastro-enteritis have also been recorded as characteristic in some epidemics. In an appreciable number of the more intensely acute and rapidly fatal of the Fulham Military Hospital 1915–1918 series of cases of cerebrospinal fever (Charles Gray and Carnegie Dickson's Reports to the War Office), hæmorrhage into the suprarenal medulla—so-called "suprarenal apoplexy"—resembling that not infrequently seen in pre-antitoxic days in the suprarenals of children dying of diphtheria, was a noteworthy feature.


(A)

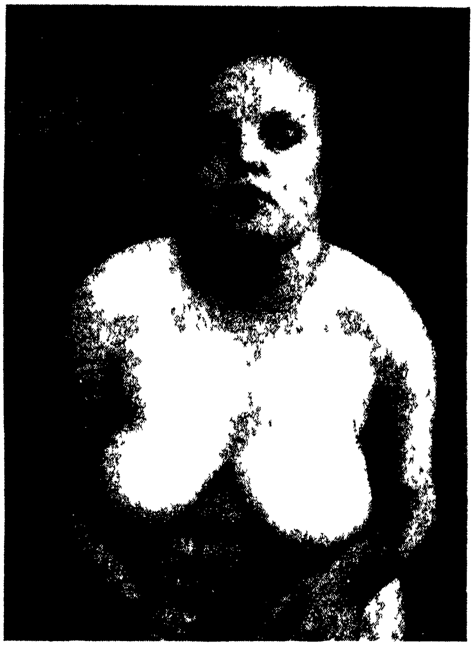

(B)

FIG. 595. *Hypopituitarism, with dwarfing and adiposity,* in a girl of sixteen, due apparently to compression of the hypothalamus, and of the pituitary from above by an *internal hydrocephalus* resulting from sealing-up of the foramina in the ependymo pial roof of the fourth ventricle *by a previous attack of meningococcal meningitis.* (W.E H. case, by courtesy of Dr. T. Rowland Hill.)

In the central nervous system, practically any part, including the brain-substance itself (*i.e.*, as an encephalitis), may in individual cases become involved, and possible complications are many and serious. The optic nerve is affected by the great rise of intracranial pressure leading to compression of its central vein and the production of papillœdema or œdematous swelling of the nerve-head. Occasionally, the optic nerve itself, and also not infrequently certain of the other cranial nerves, especially the sixth and third, are directly involved in the inflammatory process. The inflammation may spread along the pia-arachnoid sheath of the optic nerve into the eye, producing choroido-iritis or iridocyclitis ; and in some cases an inflammatory affection of the fifth nerve leads to keratitis and purulent conjunctivitis. Deafness is not uncommon, and is due in most cases to inflammation, usually bilateral, of the labyrinth or of the eighth nerve in the internal auditory meatus.

Secondary chronic and slowly progressive internal hydrocephalus may result from the sealing-up of the foramina in the ependymo-pial roof of the fourth ventricle (p. 966) ; and one of the more remote consequences of this may be the gradual compression of the pituitary by the distended floor of the third ventricle and infundibulum, leading to the production of the syndrome of hypopituitarism described on p. 808 *et seq.* (*see also* Fig. 595, p. 989), combined, it may be, with symptoms due to pressure upon the hypothalamic region.

Subacute and **Chronic Meningococcal Septicæmia,**[1] lasting perhaps for several months, and in which the organism may be cultivated from the blood, is now recognised as a distinct clinical entity, reacting favourably to treatment by the intravenous injection of antimeningococcal serum or, still more successfully and rapidly, to the administration of soluseptasine, sulphapyridine or sulphathiazole. The symptoms are headache, intermittent pyrexia, joint-pains and a maculo-papular or polymorphous rash ; and in the past the true nature of the infection has sometimes been mistaken for "rheumatic fever," "erythema nodosum," "influenza," or even "trench-fever." Kennedy [1] draws attention to the occurrence of **erythema nodosum,** *e.g.*, over the shins, as a point of diagnostic importance in relation to meningococcal infections. Unless accompanied by meningitis as a complication, the examination of the cerebrospinal fluid on lumbar puncture will be negative ; but meningitis, as well as endocarditis, nephritis and epididymitis and the other complications liable to occur in the more acute form of the disease, may supervene in these more chronic cases. Such instances of chronic meningococcal septicæmia are found especially during and after epidemics of meningococcal meningitis.

Posterior Basal or **Post-Basic Meningitis** ("**Cervical Opisthotonus of Infants**" of Gee and Barlow, 1878 ; and of G. F. Still, who, in 1898, described the presence of the organism—a "diplococcus"—now believed to have been identical with the meningococcus) is a condition now regarded as a variety of **meningococcal** infection. It is not uncommon in infants and young children, and was called "post-basic" from the fact that the exudate, though sometimes extending more widely, tends to remain confined to, and be most marked over, the posterior part of the base of the brain. Though in some instances the onset may be acute, it is as a rule less so than in the more typical cases of acute cerebrospinal meningitis. Its duration is more protracted, the exudate becomes firmer and the changes in the membranes more chronic in character than in the typical acute purulent infection. In the cerebrospinal fluid and the surface exudate itself, the intracellular Gram-negative cocci are often scanty and difficult to demonstrate. Blocking of the foramina in the roof of the fourth ventricle, leading to the production of hydrocephalus, is of frequent occurrence ; and the other phenomena and sequelæ are indistinguishable from those of the subacute or chronic forms of meningococcal meningitis, the differences depending upon variations in the virulence of the meningococcus and in the resistance of the individual patient to its attack.

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[1] "Meningococcus Septicæmia," by Col. J. C. Kennedy, *Jour. Roy. Army Med. Corps*, 1926, **47**, 6 : "Chronic Meningococcus Septicæmia," by E. Appelbaum (New York), *American Journal Medical Science*, 1937, **193**, 96, and another paper with the same title by A. W. Stott and W. S. C. Copeman, *Lancet*, 1940, **i**, 1116.

INFLAMMATION OF THE SPINAL MENINGES:

Much of the description of the inflammatory lesions of the cranial meninges (pp. 978 to 990) already given, as well as a certain amount of what follows in subsequent sections, applies equally to meningitis attacking the membranes of the spinal cord, and in many instances the two conditions are each part of a single widespread infective process. In the following section, a few points referring to some of the lesions, more particularly as they affect the spinal meninges, are given.

(*a*) **Of the Dura-Mater.** Inflammation of the external surface of the dura may be the result of the direct extension of the inflammatory process from neighbouring structures, for example an abscess in bone, or a septic focus such as a bed-sore. The condition may be suppurative and the vertebral canal become filled with semi-purulent fluid, often mixed with blood. The dura-mater is swollen, and dark-greenish or livid in colour. Secondary infection of the pia-arachnoid generally follows.

"**Pachymeningitis hypertrophica**"—"**pachymeningitis hyperplastica**" would be a more accurate descriptive term for it—is commonly syphilitic in origin, and is found especially in the **cervical** region. The inner surface of the dura gradually becomes thickened by the formation of concentric layers of fibrous tissue (Figs. 605–7, pp. 1006–7). Adhesion to the subjacent arachnoid and pia-mater, which also is thickened, is common. The condition causes pressure-atrophy of the cord, and of the nerve-roots from narrowing of the spinal foramina, together with secondary degenerative changes both in the cord and in the peripheral nerves.

"Pachymeningitis hæmorrhagica interna chronica" is a term sometimes applied to the series of changes supervening in **subdural hæmorrhage** or **hæmatoma.** In the spinal canal it is rarer than the corresponding lesion in the cranium (p. 974 *et seq.*), and in neither instance is the condition inflammatory in nature. The name, as already pointed out on p. 977, is therefore inappropriate.

(*b*) **Of the Pia-Arachnoid.** We include with the pia-mater the arachnoid, which, though not in such intimate association with it over the cord as in the region of the brain, yet in disease is generally associated with it and exhibits similar pathological changes. **Spinal leptomeningitis** is frequently secondary to, or an extension of, cerebral meningitis. Sometimes, however, it arises independently, as a result of local inflammatory processes, which, by their extension upwards, in an analogous way lead to a secondary involvement of the cerebral meninges. The pia is swollen and injected, and numerous small hæmorrhages are seen in it. The arachnoid is congested, and there is excess of fluid—at first clear, but later semi-purulent—in the subarachnoid space. The exudate, if purulent, is most abundant over the dorsal aspect of the cord. The process may spread to the dura and to the spinal cord itself, giving rise to myelitis. Spinal leptomeningitis may be due to any of the organisms which have already been enumerated as causing cerebral meningitis—streptococci, pneumococci, meningococci and the tubercle bacillus being among the more important of these.

Localised collections of fluid in the meninges, simulating cysts (**meningeal cysts: meningitis serosa**), are sometimes formed as the result of previous focal meningitis (p. 1021 and Fig. 618, p. 1022).

SECTION IV

TUBERCULOUS DISEASE OF THE CENTRAL NERVOUS SYSTEM: (NEUROTUBERCULOSIS)

TUBERCULOUS MENINGITIS. The **incidence** of this particular manifestation of tuberculosis varies greatly in different countries and localities, and in some areas it is still common. Though found most usually in children and young persons, it may occur at any age. Statistics show, however, that it is infrequent during the first three, or according to some records the first six, months of life, but thereafter it becomes increasingly common during the first decade, with its maximum incidence between the ages of eighteen months and five or six years. It is equally common in the two sexes. Either the **human** or the **bovine type** of the bacillus may be found in individual cases, the type varying, not only with such factors as the age of the patient and site of the primary infection, but also the geographical area and environment, and especially exposure of the patient to ingestion of infected cow's milk or association with human cases of phthisis.

In the earlier stages, the tuberculous exudate, on post-mortem examination, often at first sight appears to be localised to the base of the brain and limited perhaps to the interpeduncular space and the area immediately around it; but, in cases which survive for a longer period, the exudate spreads to parts in continuity with these—backwards over the posterior surface of pons, medulla and cerebellum: laterally along the lateral (or Sylvian) fissures, etc.: and forwards between the hemispheres and over the corpus callosum: and also into the substance of the brain along the sheaths of the vessels at the perforated spots. Thus the condition may come ultimately to involve a very considerable surface area of the brain, extending perhaps to the vertex. The **exudate** may at first be only slightly turbid and opaque, but later it becomes yellowish or slightly greenish-yellow in colour. It is never definitely purulent. Tubercle-granulations are present in the **leptomeninges,** though in early cases they may be so minute as to be invisible to the naked eye, but may be seen with the aid of a strong hand-lens. Sometimes they are more in evidence **along the vessels** in the depths of lateral (Sylvian) fissures or adjacent sulci and along the sheaths of the arterial branches which enter the brain-substance at the perforated spots, than at the base. In doubtful cases the membrane should be viewed under a low power of the microscope. As in meningococcal meningitis, various **cranial nerves** may come to be involved by the spread of the infective process. Thus the optic nerves and the eye itself may be attacked, with the occurrence of miliary tubercles in its choroid coat; or the movements of the eye may be affected by involvement of the third, fourth or sixth cranial nerves. For a detailed account of tuberculous lesions of the eye itself, text-books of ophthalmology should be consulted.

The bacilli in most instances reach the brain probably by way of the **blood-stream,** which they may enter from some breaking-down tuberculous lesion in the thorax, abdomen or elsewhere—*i.e.*, a condition of **tuberculous bacteræmia,** which may or may not at the same time give rise to generalised acute miliary tuberculosis (pp. 62, 553 and footnote on p. 1038). Even in the latter, *i.e.*, the acute generalised, condition, the tuberculous lesions in the brain may at first be scanty; but later these break down and discharge the bacilli **into the subarachnoid space** in numbers sufficient to produce the typical abundant exudative meningitic lesion. Several observers,[1] both in Britain and America, have recorded a number of individual cases in which the conditions of **generalised miliary tuberculosis** and **tuberculous meningitis** have each occurred *independently* of the other; but, in as many as 80 per cent. in several large series of reported cases, *both* have been found together. There is, therefore, undoubtedly a close relationship between the occurrence of these two manifestations of tuberculosis, but there has of late been a tendency to depart from the previously accepted view that tuberculous meningitis is necessarily, or even usually, merely part of an acute miliary spread like that seen in the liver or spleen. It now appears probable that a **blood-borne infection** is more likely to result in the production in the brain of a *few* or merely *moderate numbers* of **scattered caseous tubercles,** *i.e.*, a limited infection producing a localised lesion in connection with, say, pial vessels situated in a cerebral or cerebellar sulcus, or in the choroids (Fig. 599, p. 997), or in the brain-substance. In whatever part of the brain the infection may have been thus implanted, the active spread in the subarachnoid space speedily reaches and comes to affect the **basal arachnoid cisterns,** and hence the apparent early localisation of the surface meningitis in and around these at the **base** of the brain. In an analogous way, the early blood-derived caseous foci may be situated in the **choroid plexuses** or in the substance of the **ventricular wall**; and here again rapid spread will follow the breaking-down of these and the discharge of the bacilli into the ventricular system by which the infection is carried to the posterior basal region of the brain, just as in the case of meningococcal meningitis (p. 983). This view appears to be confirmed by the results of experiments in rabbits in which the intravenous injection of tubercle bacilli, *i.e.*, a pure blood-infection, does *not* lead to the production of typical meningitis.

In the human subject, the sequence, therefore, appears usually to be that (i) the bacilli obtain access to the blood-stream from some focus elsewhere in the body; (ii) the production of single or scattered sub-pial or other caseous nodules in the brain takes place; and (iii) by the breaking-down of any of these, and the ensuing concentrated inoculation of the subarachnoid space or ventricular system and spread to the basal cisterns, acute tuberculous meningitis in its characteristic basal situation is produced. Less commonly, the infection reaches the brain from local tuberculous lesions of the bones of the skull, *e.g.*, the temporal bone; and in certain instances the spinal theca is infected from tuberculous disease of the vertebræ (Pott's disease, pp. 66–8, 998–9, and 1219: and *see also* Fig. 600, p. 999).

The Cerebrospinal Fluid in Tuberculous Meningitis. Clinically, it is sometimes difficult to determine whether an actual and active tuberculous meningitis is commencing, or whether the condition is due merely to the presence of a sub-pial caseous nodule which has not yet led to serious meningitic involvement and which may be becoming subacute or chronic. In the latter, a few cells and perhaps on careful search even an occasional tubercle bacillus may be detected in the lumbar-puncture fluid; and, as the localisation and retrogression of the lesion may still be possible without acute dissemination of bacilli into the subarachnoid space, such a course of events may account for the occasional instances recorded as " recovery from tuberculous meningitis in which tubercle bacilli have been found in the cerebrospinal fluid."

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[1] "The Pathogenesis of Tuberculous Meningitis," by A. R. Rich and H. A. McCordock. *Bulletin Johns Hopkins Hospital,* 1933, **52,** 5; "Tuberculous Meningitis in Children," by J. W. S. Blacklock and M. A. Griffin, *Journal Pathology and Bacteriology,* 1935, **40,** 489; "Tuberculosis of the Central Nervous System with special reference to Tuberculous Meningitis," by A. R. Macgregor and C. A. Green, Edinburgh, *Journal Pathology and Bacteriology,* 1937, **45,** 613 (which see for further references).

In typical tuberculous meningitis, the fluid is under increased pressure and may for a time to the naked eye appear clear and colourless whilst the pleocytosis is still moderate in degree, say 50 or 100 cells per c.mm.; or there may be a faint and just visible " ground-glass " turbidity if the cells rise to 400 or 500 or more. In rare cases, the cells increase to several thousand and then produce a frankly turbid fluid. Even the clear and colourless fluid from an early case tends on standing to develop a fibrinous **spider-web clot** which, on its removal from the fluid, contracts into a small firm mass; and, in teased film-preparations or in paraffin-sections stained by the Ziehl-Neelsen method, tubercle bacilli may be found in it. The bacilli may be present in very small numbers and be discovered only after prolonged search, or they may be found in moderate or even in enormous numbers; and their presence can also usually be successfully demonstrated by culture and by animal-inoculation. The cells present are mainly mononuclear—**lymphocytes** or cells of lymphocytic type, usually with a varying number of slightly larger mononuclears, but, especially in severe cases which run an acute course, a few or even considerable numbers of **polymorphonuclear leucocytes.** Polymorphs have also been observed to increase in number following upon lumbar puncture, a feature noticeable in some cases re-examined a day or two after the previous withdrawal of cerebrospinal fluid. Later, and particularly in the more chronic cases, the lymphocytes greatly predominate.

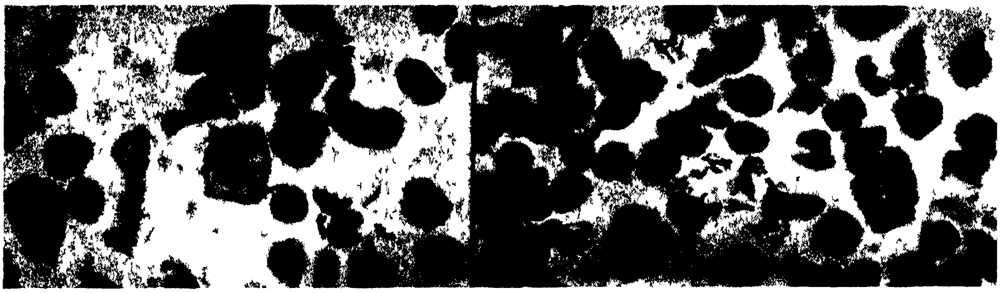

FIG. 597. *Spinal exudate in tuberculous meningitis*: showing numerous tubercle bacilli in an exudate composed of lymphocytes, small endothelial cells and an occasional polymorphonuclear leucocyte. On the tenth day of the clinical illness, the cells in the cerebrospinal fluid numbered 205 per c.mm.; but, just before the death of the patient, an adult male, the fluid, from which this preparation was made, contained 34,000 cells per c.mm. (Ziehl-Neelsen's stain. × 1,000.)

As noted on p. 988, the appearance of large numbers of polymorphs is also an almost constant feature in those cases of tuberculous meningitis which have been erroneously diagnosed as cerebrospinal fever, and into the spinal theca of which antimeningococcal serum has been injected—a similar phenomenon occurring after the intrathecal injection of antimeningococcal serum into cases of cerebrospinal syphilis. The cell-picture so produced by such injection of serum into tuberculous or syphilitic meninges may, therefore, closely simulate, and be mistaken for, that of true acute cerebrospinal meningitis, meningococci being, however, absent.

Though an increase in the number of **lymphocytes** in the cerebrospinal fluid is, in the absence of a positive Wassermann reaction, suggestive of tuberculous meningitis, the cytological picture in benign lymphocytic choriomeningitis (pp. 116 and 1000), except for the absence of tubercle bacilli, closely simulates that of a tuberculous infection. Meningeal symptoms or actual meningitis may occur also in mumps, measles (pp. 117–118), etc., and in these an increase of lymphocytes in the fluid is a distinctive feature. A similar increase is characteristic of the various manifestations of syphilis of the central nervous system, for example in general paresis, tabes dorsalis and syphilitic meningo-encephalitis ; but it must not be forgotten that a tuberculous infection may be implanted upon such syphilitic and other conditions. The pronounced **diminution** in the amount of **sugar,** and more particularly of the **chlorides** —to less than in any other pathological condition (pp. 963–4)—in definite cases of tuberculous meningitis is valuable additional diagnostic evidence, as contrasted with the findings in syphilis, and also in lymphocytic choriomeningitis and other virus-infections, in which the chlorides and sugar in the fluid are as a rule little if at all affected. Merritt and Fremont-Smith [1] (1938) state that this reduction in the amount of chlorides in the cerebrospinal fluid in tuberculous meningitis is dependent upon a corresponding diminution of the chlorides in the blood-plasma. In the case of sugar, the decrease seems to be due, not to any lowering of the permeability of the " blood-brain barrier " (pp 953 and 962–3), but, as evidenced by a corresponding **increase** in the amount of **lactic acid,** to breaking-down of the sugar **in** the fluid itself under the action of the leucocytes rather than of the tubercle bacilli ; though, as pointed out on p. 963, in some bacterial forms of meningitis, certain saccharolytic organisms such as *Bacterium coli* take an active part in causing the diminution of the sugar or even its complete disappearance. The **increase in coagulable protein** in the fluid varies greatly, but in the majority of cases lies between 50 mgr. and 500 mgr. per cent. A moderate excess of **globulin** is usually present, together with free complement and perhaps some hæmolysin. The Lange-curve is of meningitic end-zone type (p. 964), and, as already mentioned, the Wassermann reaction is negative.

On examining the **brain** *post mortem,* the convolutions are found to be flattened, and the **pia-arachnoid** has a dry and glazed appearance. The exudate with its minute tubercle-granulations, as already noted, may be present. On cutting the brain, the **ventricles** are seen to be distended with clear, or more usually slightly turbid, fluid, the amount of distension varying greatly, but sometimes so considerable as to constitute an **acute hydrocephalus.** This distension is most pronounced in the lateral ventricles, the walls of which are softened. This accumulation of fluid is due in part to the tuberculous exudate derived from the inflamed choroids and ventricular wall, and in part to the occlusion of the communications between the ventricular system and the subarachnoid space by the inflammatory changes in the region of the fourth ventricle. The softening of the walls and adjacent brain-tissue is due, not merely to the mechanical accumulation of the fluid and the action of toxins, but to actual tuberculous endoventriculitis and encephalitis associated with a tuberculous endarteritis which causes obstruction to the vascular supply. A more diffuse form of **encephalitis,** occasionally hæmorrhagic, is sometimes associated with the tuberculous meningitis.

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[1] " The Cerebrospinal Fluid," by H. Houston Merritt and F. Fremont-Smith (Boston City Hospital). W. B. Saunders Company, Philadelphia and London, 1938, p. 105.

Microscopical examination of sections of the surface meningeal exudate, cerebral or spinal, and of the subjacent nervous tissue, brings out the various histological features already described under general tuberculosis (p. 58 *et seq.*), modified by the nature of the structures attacked. The spread in the tissues themselves is largely perivascular, *e.g.*, around the pial vessels, with the usual aggregations of lymphocytes, plasma- and other mononuclear cells, and the formation of endothelioid and giant-cells, often arranged in small nodular masses situated to one side of or around the vessel, with invasion of the media, and accompanied or followed by obliterative changes in the intima and lumen. The tuberculous process is liable to spread widely along the vessels and in the meshes of the leptomeninges, and may produce a certain amount of superficial tuberculous encephalitis or myelitis. Analogous changes take place in the walls of the ventricles, with the presence of tuberculous choroiditis and ependymitis, and in any of these lesions varying numbers of tubercle bacilli may be found (Figs. 597 and 599 D).

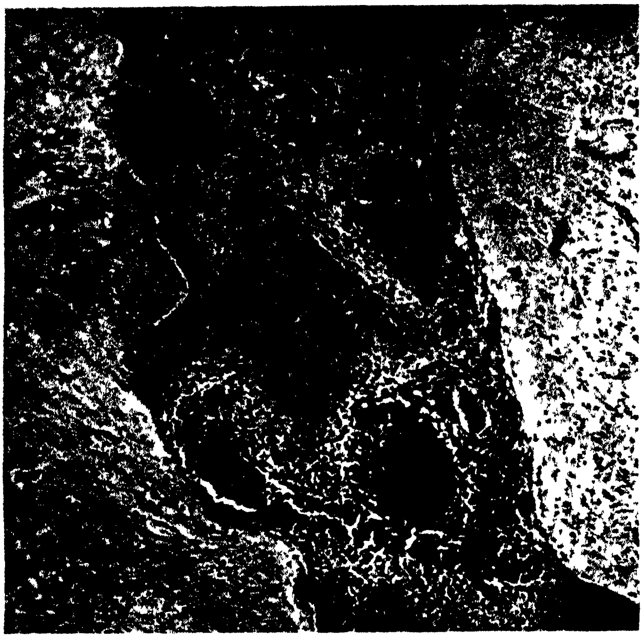
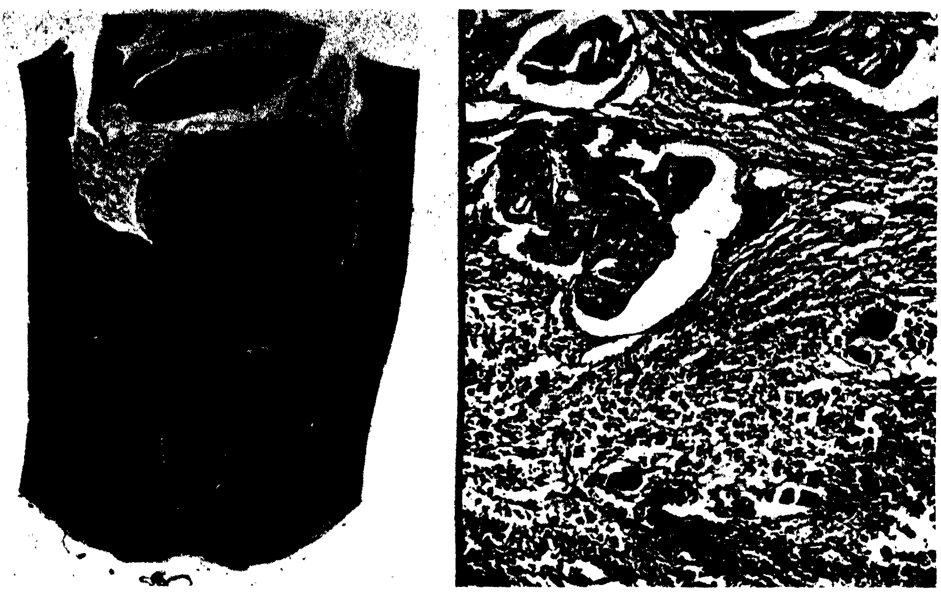


FIG. 598. *Brain : tuberculous meningitis.* Section across a cerebral sulcus showing acute tuberculous exudate, chiefly around pial vessels. (By courtesy of Dr. Agnes Macgregor.) (Hæmatoxylin and eosin. × 75.)

If search be made for them, the original larger single or perhaps several

Fig. 599. *Brain: a small "tuberculoma" in choroid plexus of fourth ventricle in a man aged thirty years.*

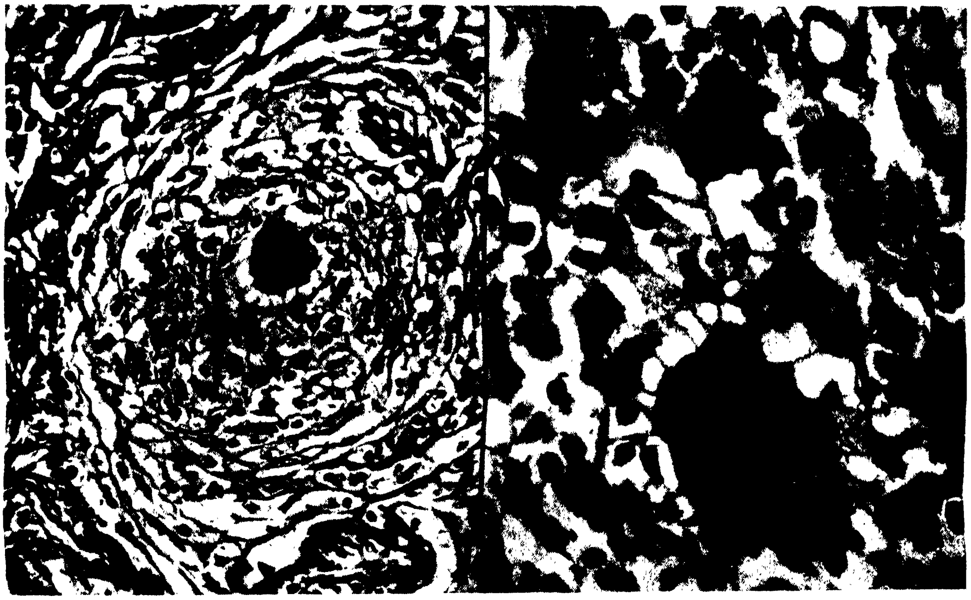


(A) × 2⅓

(A) Section, only slightly magnified, to show site of chronic tuberculous nodule in choroid, distorting and invading floor of ventricle. (Mallory's connective-tissue stain.)

(B) × 100

(B) Low-power view of periphery of nodule developing in choroid, part of which is seen above undergoing destruction, with tuberculous granulation-tissue and giant-cells below. (Hæmatoxylin and acid fuchsin.)



(C) × 300

(C) High-power view of a small tuberculous giant-cell system situated in the choroid, parts of the latter being seen at the periphery to the left of the figure. (Hæmatoxylin and acid fuchsin.)

(D) × 950

(D) Giant-cells and endothelioid cells of the granulomatous tissue containing tubercle bacilli. Ziehl-Neelson method. (W.E.H. case.)

scattered nodules of older and more chronic caseous tubercle, the hæmatogenous origin of which has already been described, may be detected, in the depths of a sulcus, in one of the choroid plexuses (Fig. 599), or elsewhere in the nervous tissue itself. These will show the changes characteristic of older tuberculous lesions (p. 63), such as caseation, partial encapsulation, etc., and are liable at any period of their development to become surrounded by a more acute spread which may then involve the ventricles or arachnoidal cisterns, and so give rise to the typical meningitic condition under discussion. The appearances at the base of the brain have been described on p. 992 *et seq*. The disease also extends downwards and involves the **spinal cord** and its **membranes**, which show changes and appearances analogous to those already described for the brain. A further description of tuberculous lesions of the cord and its membranes will be found below.

Still larger **tuberculous masses** (sometimes described as "tuberculomas") in the brain-substance are found in some cases of tuberculous meningitis, but they may also occur independently in the form of irregular tumour-like nodules in any part of the brain, but are commonest in the cerebellum. They are single or multiple, and vary in size, sometimes reaching an inch or more in diameter. They are found especially in young people, and on naked-eye examination are clearly outlined and show a yellowish caseous centre. On microscopical examination, the nodule is composed of an amorphous caseous mass, with a peripheral zone of giant-celled tubercle-granulations, which gradually merge into the surrounding brain-substance. These "tumours" may reach the surface and give rise to tuberculous meningitis, a complication which may also follow operative interference with them; or, by pressure on the straight sinus or on the great cerebral vein of Galen, they may cause dilatation of the lateral ventricles and chronic hydrocephalus. They also lead to serious results by infiltrating or pressing upon important parts of the brain.

TUBERCULOSIS INVOLVING THE SPINAL CORD. For descriptive purposes, tuberculosis of the spinal cord and of its membranes cannot be separated from one another. Several varieties of the condition occur.

i. **Tuberculous Meningitis associated with Caries of the Vertebræ (Pott's Disease).** Tuberculous caries (p. 66) may be limited to one vertebral body, or it may affect several. Occasionally, it commences in the transverse process and affects the vertebral body secondarily. It is found at any part of the spinal column, but is of most frequent occurrence in the lower thoracic and upper lumbar regions. The tuberculous disease, after destroying the anterior common ligament, reaches the dura, the outer surface of which becomes thickened and infiltrated. The tubercle-granulations extend into the substance of the dura, and at a later period give rise to extensive tuberculous infiltration of its inner surface. Farther extension takes place, and the pia-arachnoid and the various nerve-roots become involved. On account of the accumulation of tuberculous material in the canal, compression of the spinal cord (Fig. 600), with consequent ascending and descending degenerations, may follow. By reason of the destruction of the vertebral bodies, curvature or, it may be, a distinctly angular deformity of the spine—sometimes described as "angular curvature" (p. 1219)—with displacement of, and pressure on, the spinal cord, takes place, and either myelomalacia or actual tuberculous myelitis is produced. Death supervenes, in some cases, from sudden dislocation of the diseased vertebræ. This may happen especially where the odontoid process, or the transverse ligament which holds it in position, becomes eroded by the disease. In tuberculous caries, localised patches of myelomalacia may occur even apart from pressure. These are due probably to interference with the blood-supply (ischæmia) or to the action of the toxins.

ii. **Tuberculous pachymeningitis,** unassociated with disease of the bone, sometimes occurs, especially in the cervical region of the cord. The dura-mater and the surrounding structures become swollen and infiltrated with tubercle-granulations.

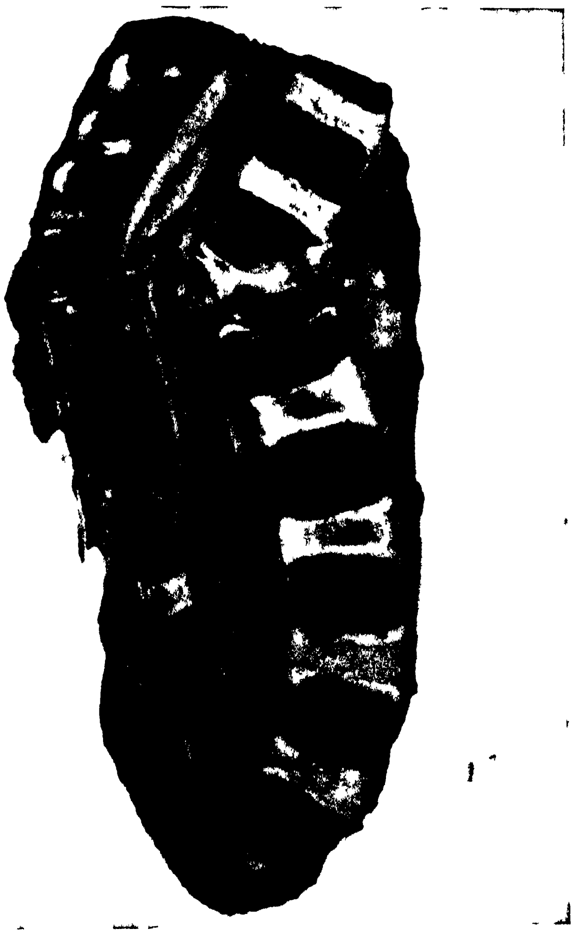


FIG. 600. *Tuberculous (Pott's) disease of bodies of vertebræ* producing pressure on the spinal cord. (The nerve-roots opposite the lesion have been accidentally displaced.)

iii. **Tuberculous Leptomeningitis.** This is, as has been stated above, generally associated with tuberculous cerebral meningitis. Minute, grey tubercle-granulations are seen on the surface of the pia-mater, at first especially in the cervical or the lumbar region, but, later, throughout the whole length of the cord, among the nerve-roots of the cauda equina, and also on the inner surface of the dura. The subarachnoid space may become distended with fluid containing numerous cells, amongst which, as noted on p. 994, lymphocytes usually predominate. The tubercle bacillus itself is sometimes only with difficulty demonstrated in the fluid; but is found, sometimes in enormous numbers, in the granulations in the meninges. The other findings in the cerebrospinal fluid in tuberculous infections are described in detail on p. 993 *et seq.*

iv. **Tuberculous granulations** are rarely found in the **substance of the cord** itself, without primary affection of the meninges. When present, they are generally in the form of large, solitary, conglomerate tubercles, which give rise to areas of softening or myelomalacia.

ACUTE LYMPHOCYTIC CHORIOMENINGITIS ("**LCM**") is a virus-produced disease (p. 116) which has only comparatively recently been recognised as a definite pathological entity. It has been described under numerous other synonyms, including "acute aseptic meningitis" (Wallgren's[1] "*méningite aseptique aiguë*," 1925), "benign lymphocytic" or "serous" meningitis; but it is likely that at all events some of these constitute a **group** of conditions capable of still further subdivision, and, from certain of them, a virus apparently immunologically distinct from that of typical acute lymphocytic choriomeningitis has been obtained (MacCallum and Findlay,[2] 1939). The disease is widely distributed geographically: and—although nervous symptoms do not develop in a considerable proportion (more than 50 per cent., it is said) of patients infected by the specific virus—in characteristic examples of the condition, **lymphocytic meningitis** is a febrile disease often commencing with an influenza-like respiratory catarrhal attack or coryza, followed by symptoms of meningitis and by distinctive findings in the cerebrospinal fluid; whilst, in contra-distinction to tuberculous meningitis in which the prognosis is grave, it usually runs a benign course with recovery. It is commoner in children and young persons than in older people, and it is likely that, as in poliomyelitis, the immunity of later life has been produced by a previous subclinical infection. Fatal human cases being thus exceptional, the morbid anatomy of the condition in man has not yet been fully investigated. "**LCM**" itself seems now definitely proved to be due to a **virus** which has been isolated from the nasopharynx of these patients, as well as from" carriers." This virus, although apparently, in some reported cases,[2] capable of producing encephalitic and myelitic lesions, is distinct from that of epidemic encephalitis. Small rodents such as the common grey mouse are believed to act as the natural reservoir of the infection, the urine of infected mice having been found to be capable of transmitting the infection, and the virus persisting in virulent form in the brains of these rodents for several months, and causing an epizoötic amongst colonies of mice lasting, perhaps, for at least four months. Mice and dogs can act as "healthy carriers." Accidental laboratory infection of the human subject with this virus by way of the conjunctival sac has been recorded,[1] with an incubation-period of ten days before the onset of an "influenza-like" febrile attack lasting a few days. After a temporary improvement, the temperature again rose on the ninth day of the illness, with headache, nausea and vomiting, and neck-rigidity. There was marked loss of weight, and convalescence was slow, extending over several months. Specific complement-fixation was obtained between antibodies in the patient's serum and the choriomeningitis virus. This virus has been grown artificially upon the chorio-allantoic membrane and brain of the developing chick; and, on inoculation into mice and monkeys, produces an intense meningitis, characteristically basal in distribution, and, in the majority of the experimental animals, an endoventriculitis involving the choroids and the ependymal lining of the ventricular system—hence the appropriate term "**choriomeningitis**" now used to describe the disease. The perivascular cell-infiltration in the brain-tissue, characteristic of epidemic and certain other forms of viral infection, is apparently *not* a feature of this disease.

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[1] Arvid Wallgren: "Une nouvelle maladie infectieuse du système nerveux central?" *Acta Pædiatrica*, Upsala, 1925, **4**, 158.

[2] "Lymphocytic Choriomeningitis," by F. O. MacCallum, and G. M. Findlay, *Lancet*, 1939, **i**, 1370 (and Editorial, *ibid.*, 1388). These observers describe a case with paralytic symptoms in the lower limbs resembling those of anterior poliomyelitis. The mosquito *Aëdes ægypti* can transmit the virus by bite four to fifteen days after an infective feed (Coggleshall, quoted in *Lancet* review). In a subsequent editorial (*ibid.*, 1942, **i**, 741-2), it is stated that two-thirds of the cases are still of an unknown ætiology; and the other third are probably caused by one of the three viruses so far isolated from these cases—known respectively as the **viruses of lymphocytic choriomeningitis: of pseudo-choriomeningitis: and of "la maladie des porchers"** ("swineherds' disease"). Some cases of the group may simulate and be mistaken for "influenza," "poliomyelitis," "epidemic encephalomyelitis," or "tuberculous meningitis."

The clinical signs and symptoms being those of a meningitis, it is possible that the less transient cases may have in the past not infrequently been mistaken for tuberculous meningitis (compare pp. 960 *et seq.* and 995), especially those cases which have been described as "recoveries" from the latter condition. Tubercle bacilli and other bacteria are *not* found, the **chloride**-content of the cerebrospinal fluid is usually **normal, sugar** not appreciably diminished, and, as already noted, the prognosis of the disease is favourable.

The **cerebrospinal fluid** is under increased pressure: clear and colourless, or sometimes slightly turbid; and occasionally shows a spider-web coagulum on standing. **Cells** are usually from 100 to 300, but vary from 50 to over 2,000 per c.mm. They are at first largely polymorphonuclears, but in a day or two these are replaced by lymphocytes, which may by the end of a week be the only type of cell found, except perhaps for an occasional larger monocyte. In from 4 to 6 weeks from the onset, the total cell-count has usually fallen to 10–15 cells per c.mm. The **total protein** varies from 50 mgr. to 300 mgr. per 100 c.cm., with a negative Wassermann reaction in the fluid and blood. Agglutination-reactions with organisms of the enterica and undulant-fever groups are negative. Acute lymphocytic meningitis has to be distinguished, not only from tuberculous and syphilitic meningitis, but also, especially in the tropics, from dengue, influenza, spirochætosis icterohæmorrhagica and lead-encephalopathy—the last-mentioned condition said to be common especially among Chinese in the Far East, in both children and adults, owing to the extensive use of toilet and face-powders containing lead.

Bacillus Monocytogenes Infection. A form of suppurative leptomeningitis, characterised by the presence in the cerebrospinal fluid of an excess of **mononuclear cells,** mostly large in size, and approximating to or even outnumbering the polymorphs which are also present, has been described as associated with the presence of a Gram-positive bacillus, *Bacterium (Listerella) monocytogenes.* In the human subject, the immediate source of infection with this organism is as yet untraced, but disease caused by it is found in cattle, sheep, rodonts and fowls. Experimental inoculation of rabbits produces a monocytosis in the blood (p. 622); and small focal lesions are found in the liver in both animals and man.

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[1] P. Lépine and V. Sautter, *Annales Instit. Pasteur,* 1938, **61,** 519.

SECTION V

SYPHILITIC DISEASE OF THE NERVOUS SYSTEM: (NEUROSYPHILIS)

The general subject of syphilitic infection, its clinical "stages," and the many and varied lesions produced by it, are discussed in the chapter on Granulomatous Diseases (p. 80). Owing to the fact that most cases are now diagnosed and treated at a comparatively early stage, the end-results of uncomplicated syphilis are less often seen *post mortem* than formerly, and this is true particularly of syphilitic lesions of the nervous system. In the pathological investigation, either clinical or post-mortem, of individual cases, it is therefore needful to ascertain, if possible, whether the patient has been treated, the nature and adequacy of such treatment, and the period or periods of the disease at which it was administered. Another important fact in this connection is that, in inadequately treated cases, the period between primary infection and the serious involvement of the nervous system is, in an appreciable proportion of patients, actually shortened, these cases also being rendered more liable to suffer from relapses.

In such cases of latent syphilis, spirochætes which have resisted treatment may survive in the more inaccessible parts of the nervous and vascular systems. Evidence has recently been brought forward to suggest that the spirochætes may also persist especially in certain of the lymph-nodes, for example those of the mediastinum or abdomen, and thence subsequently re-infect, amongst other nervous tissues, the spinal ganglia on the posterior or dorsal nerve-roots, thus producing tabes dorsalis : or they may survive in the walls of larger blood-vessels, more particularly the aorta, and so lead to the production of chronic cardiovascular syphilis.

The lesions which syphilis may produce in the nervous system are so protean in their variety and distribution that almost any form of nervous disease can be simulated. Moreover, syphilitic infection often precedes, co-exists wiht, or becomes implanted upon, other diseases such as tuberculosis, tumour, or vascular degeneration ; and syphilis itself may also predispose to the occurrence of some of these.

In the past, largely on account of the fact that the cerebrospinal fluid has not always been examined as a routine procedure, as is now the case with the blood, the frequency with which the nervous system is involved has been underestimated and it was believed that definite clinical neurosyphilis supervened in only 2½ or 3, or at most in some 5 per cent. of all cases of syphilitic infection. With more thorough methods of investigation, however, recent statistics prove that the relative proportion is much higher. Kemp and Menninger in America [1] give an incidence of just over 50 per cent. in untreated cases: over 40 per cent. in inadequately treated patients : and under 20 per cent. where treatment has been early and apparently thorough. In this particular series, the latent period between initial infection and the clinical involvement of the central nervous system was 17.6, 11.6 and 11.4 years respectively in these three classes of patients. Of over a thousand cases of primary and secondary syphilis investigated in China (Frazier and Mu,

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[1] *Bull. Johns Hopkins Hospital*, 1936, 58, 24.

1936), 13 per cent. showed clinical involvement of the nervous system in the form of acute meningeal symptoms or cranial-nerve palsies. In New York, Berens and Goldberg (1937) found the incidence of eye-lesions believed to be syphilitic to be approximately 6 per cent. amongst 100,000 general patients.[1]

For descriptive purposes, the lesions produced in the central nervous system may be divided into two main groups :—

(A) **Meningo-vascular Syphilis,** in which the membranes, and the blood-vessels with their supporting connective tissue (*i.e.*, the **mesoblastic** elements which take part in the support and nourishment of the central nervous system), are attacked, with the production of **meningitis,** various forms of **arteritis,** and **gummatous formation.**

(B) **Parenchymatous Neurosyphilis,** in which the spirochætes invade the nervous tissues of the central nervous system directly, and thus produce the clinical picture of **general paresis** or of **tabes dorsalis**, two characteristic manifestations which tend to supervene late in the course of the disease—sometimes not until several or perhaps many years after the primary infection.

(A) MENINGO-VASCULAR SYPHILIS:

Syphilitic meningitis, with involvement of the dura, the pia-arachnoid, or both of these—either simultaneously or in sequence—may arise at any time during the period of general dissemination of the spirochætes, more particularly

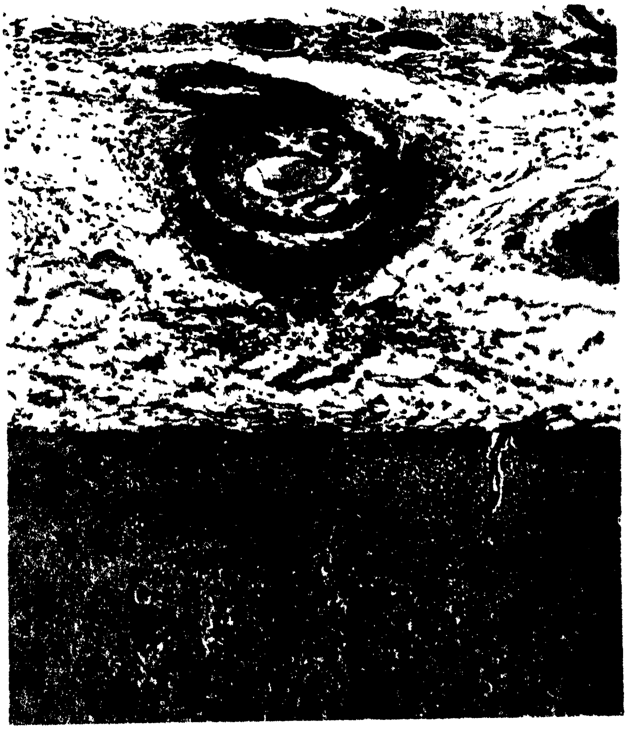

FIG. 601. *Meningo-vascular syphilis* : vertical section of junction of meninges and cerebral cortex showing syphilitic meningitis with arteritis and gummatous infiltration. (Van Gieson and hæmatoxylin. × 80.)

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[1] For an account of the clinical and therapeutic aspects of the subject, *see* " Neurosyphilis : Syphilis of the Nervous System," by C. Worster-Drought, John Bale, Sons & Staples Ltd., London, 1940.

in the secondary or early tertiary stages of the disease ; though changes in the cerebrospinal fluid indicative of a meningeal reaction are found in a certain number of patients who are still suffering from the primary sore. In these, as in early secondary cases, spirochætes may be present in the fluid, together with a slight or moderate pleocytosis and perhaps slight protein increase and altered colloidal-gold curve. In a few instances, the occurrence of a positive Wassermann reaction in the fluid *before* its appearance in the blood has been recorded.[1] The process, once started in the meninges, is apt to continue and be progressive, unless cut short by efficient treatment.

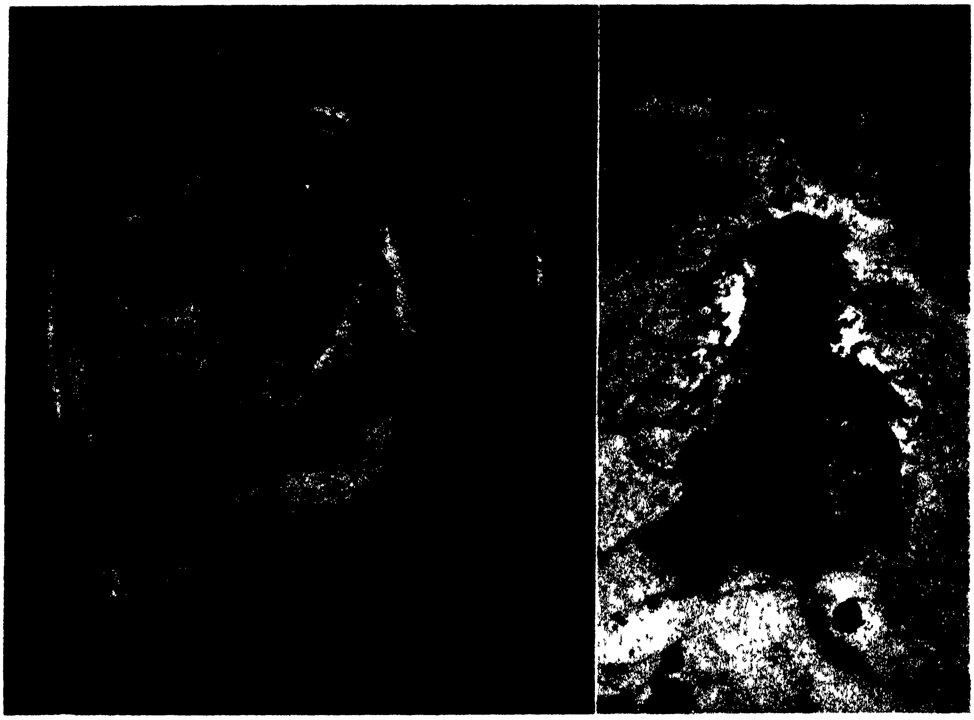
(A) (B)

FIG. 602. (A) *Gumma of skull* (macerated dried specimen) showing erosion and perforation of the bone. (B) The area of the lesion seen from inside.

The attack upon the membranes, though due sometimes to local extension from disease of adjacent bone, is caused most commonly by direct blood-borne infection. When the **dura** is involved, as a **pachymeningitis**, there may be either localised or widespread fibro-cellular thickening, gradually increasing by extension inwards, with the production of adhesions to the subjacent leptomeninges. Such pachymeningitis may cause narrowing of any of the foramina or canals by which nerves or vessels enter or leave the skull, with consequent compression of these structures. The most frequent form of infection of the membranes, however, is **leptomeningitis,** with varying degrees of gummatous infiltration in and around the vessels, producing, to the naked eye, patchy or diffuse gelatinous thickening, showing microscopically as an admixture of caseous necrosis and small round-celled infiltration (Fig. 601).

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[1] *See* Merritt and Fremont-Smith : "The Cerebrospinal Fluid," 1938, p. 112.

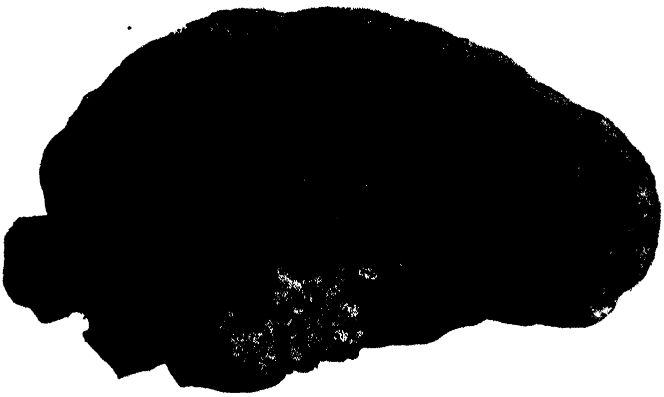
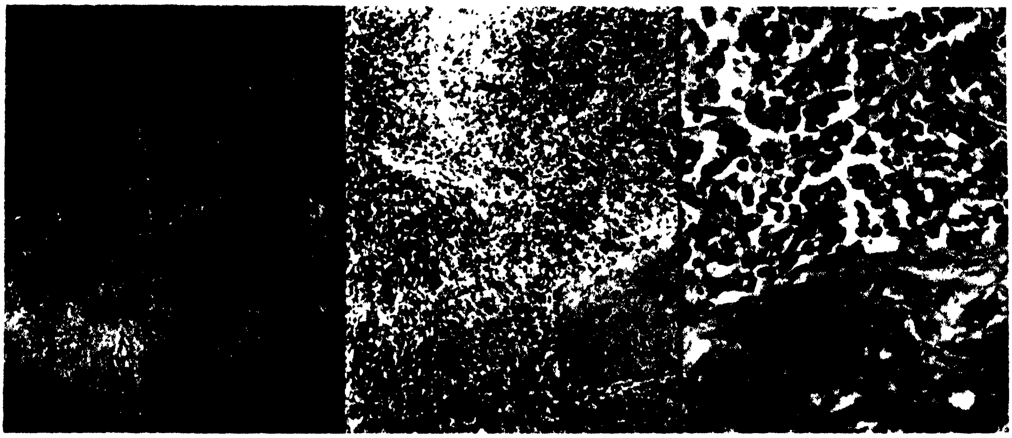


FIG. 603. *Syphilitic gumma of Brain:* mesial sagittal section, from a male aged thirty-six, with imperfectly treated syphilis. There was gradual loss of sight and progressive weakness. A *large gummatous mass* was found *post mortem* at the base of the brain, as shown in the illustration. (By courtesy of the Pathological Dept. of St. Bartholomew's Hospital.)

Large gummata,[1] single or occasionally multiple, though liable to develop at any part of the dura, occur especially in the region of the vertex : less frequently elsewhere over the hemispheres : or at the base of the brain, where they may press upon and infiltrate nerves and vessels, invading and eroding the cranial bones. Any of the cranial nerves may be attacked. The optic nerves, though liable to these forms of syphilitic lesion, are also affected

FIG. 604. *Syphilitic gumma of cerebral cortex.*



(A) × 20
Very low-power view showing necrotic centre below, and formation of peripheral gummatous granulation-tissue (the slightly darker patch) above.

(B) × 70
Low-power view of peripheral zone of granulomatous tissue round necrotic centre, a small portion of which is seen at lower right corner.

(C) × 250
High-power view showing details of syphilitic granulomatous tissue, which consists of a mixture of small round and endothelioid cells.

(Hæmatoxylin and eosin. From a preparation of the late Dr. Perdrau.)

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[1] In the past, necrotic tumours, both meningiomas and gliomas, now preserved in museums, have sometimes been mistaken for "large single gummata," but when re-examined by modern methods have been found to be neoplastic.

by the increased intracranial pressure, and papilloedema is a frequent sequel of gumma. Involvement of the third, sixth and seventh cranial nerves is common, with resulting paresis or paralysis of the muscles supplied by them. When the trigeminal is affected, various sensory disturbances in its area of distribution are commoner than motor weakness ; whilst involvement of the eighth nerve leads to impairment of hearing. In this connection it must be kept in mind that the **central nuclei** of any of these nerves are not infrequently attacked by syphilitic disease ; and also that potent drugs such as arsenic, mercury and bismuth, used in the treatment of syphilis, can themselves —especially in persons unduly sensitive to their action—produce pathological lesions, for example hæmorrhagic and other forms of encephalitis, polyneuritis, and involvement of the optic and other cranial nerves.

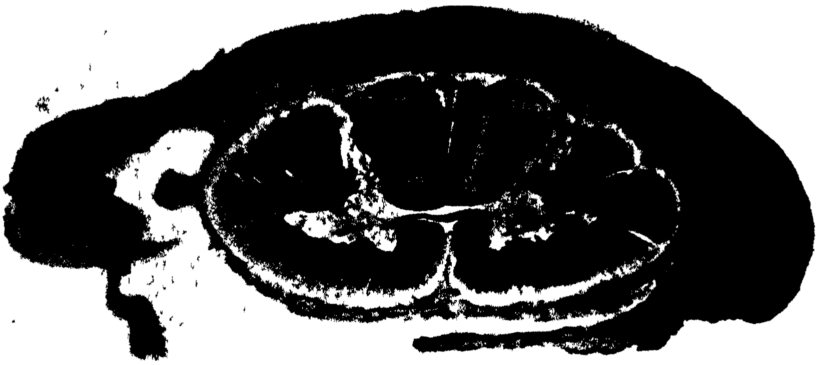

FIG. 605. *Spinal cord : syphilitic pachymeningitis* causing " compression myelitis " in a female, aged fifty-three. Transverse section of cord and thickened adherent meninges at level of 4th cervical segment. Note demyelination of periphery of cord and of a large part of funiculus cuneatus on each side. (From a preparation of the late Dr. Perdrau, stained by Weigert-Pal's and counterstained by van Gieson's methods.) (× 4½ diam.)

Thickening of the membranes of the **spinal cord** may involve nerve-roots and be associated with myelitis (Fig. 605). **Pachymeningitis,** especially the form found in the cervical region (" pachymeningitis cervicalis hypertrophica "), is most commonly syphilitic, the progressive thickening of the dura leading to the formation of adhesions to the arachnoid and the pia and to compression and damage to the cord and its nerve-roots. Implication of the dorsal (or posterior) roots leads to sensory phenomena, especially pain, and to loss of muscular tone ; whilst paresis or paralysis follows involvement of the ventral (anterior or motor) roots. **Meningomyelitis** involving both the leptomeninges and cord is found most frequently in the thoracic region, leading to compression of the dorsal or the ventral roots, with corresponding sensory or motor disturbances. Obliteration of the theca by such adhesions is an important cause of "**spinal block**" and the production of **Froin's syndrome** (p. 963). Amongst the results of syphilitic involvement of the dorsal ganglia is the occasional production of herpes zoster, perhaps from the stimulation into activity of the latent, *i.e.*, already present, zoster virus (p. 102).

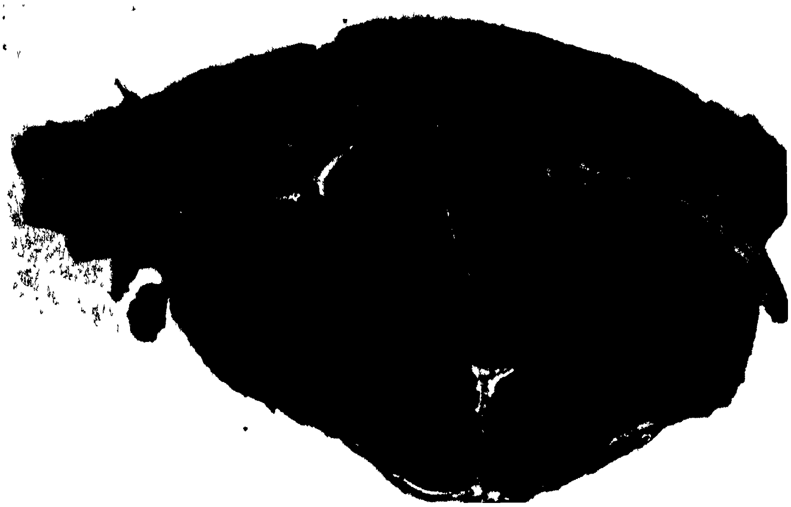

FIG. 606. *Syphilitic hyperplastic pachymeningitis* (a term preferable to " hypertrophic ") with compression of the spinal cord : transverse section through the lower cervical region showing coalescence of the greatly thickened dura-mater and leptomeninges which are adherent to the cord, over the anterior aspect of which the thickened dura has been removed. (For higher-power view of vessels marked with arrow, *see* Fig. 607 below.) (Stained by Weigert-Pal's and counter-stained by van Gieson's method.) (× 4½ diam.)

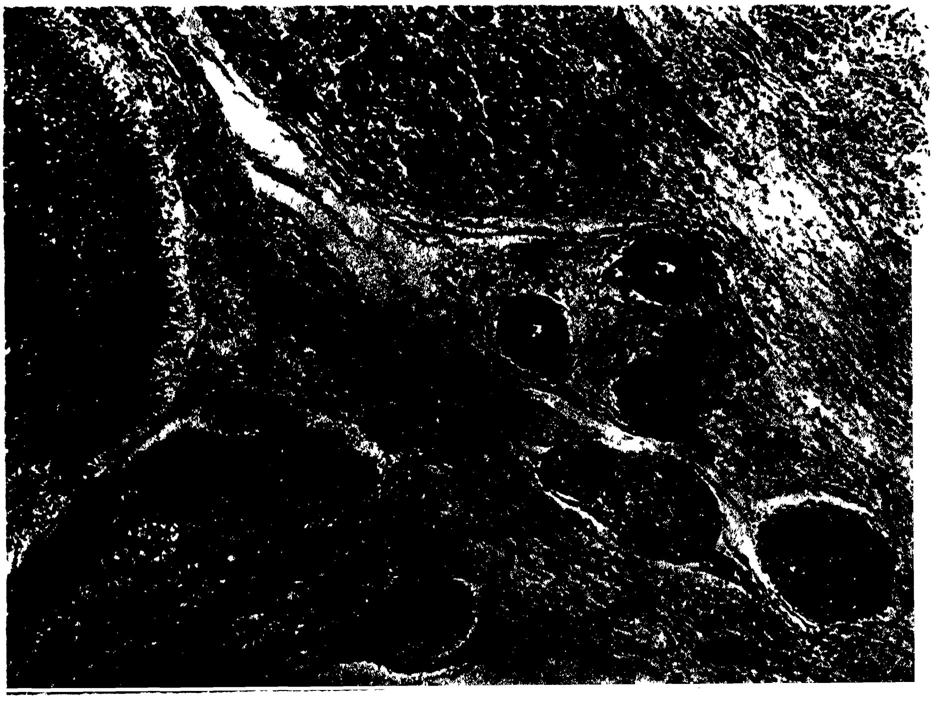

FIG. 607. *Syphilitic hyperplastic pachymeningitis* : high-power view of the three small branches of the posterior spinal artery (marked with arrow in Fig. 606 above) showing syphilitic panarteritis, especially endarteritis obliterans, the vessels being embedded in the thickened leptomeninges. Note also the patchy demyelination of the dorsal nerve-root bundles and adjacent part of the spinal cord. (Stained by Weigert-Pal's and counterstained by van Gieson's method.) (× 100.)

Syphilitic Arteritis. Any of the arteries of the central nervous system, and not merely the vessels of the membranes, may be the seat of syphilitic **endarteritis** and **periarteritis**; or if, as is frequently the case in the larger vessels, the **media** is also implicated, the condition may be termed a **panarteritis.** The basilar artery, the middle cerebrals and their branches are specially liable to be affected, the posterior cerebrals rather less frequently. Widespread involvement of the smaller arteries is common. The larger vessels show mainly atheroma (p. 484): the smaller chiefly endarteritis proliferans and periarteritis (p. 479). In rare instances there is the development of discrete nodules along the arteries, "nodose *peri*arteritis" (to be distinguished from the non-syphilitic "*poly*arteritis nodosa—perhaps better termed "panarteritis nodosa," p. 478), or, more rarely still, in the walls of the veins. The relationship of syphilis to the production of **aneurysms** is discussed on pp. 493 and 1042 *et seq.*

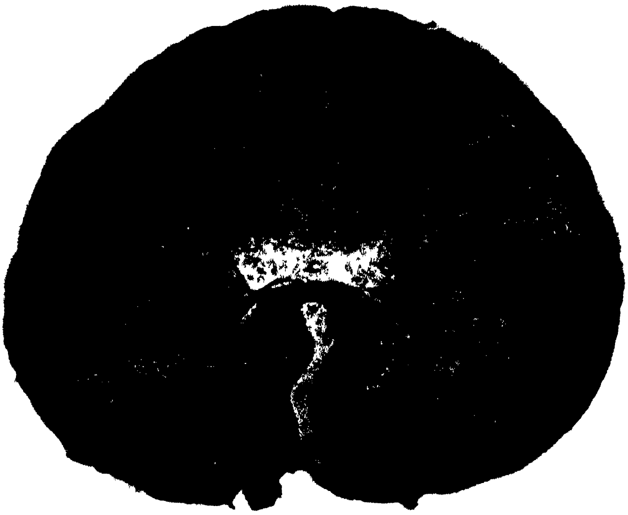

FIG. 608. *Syphilitic myelitis*. transverse section through lumbar region of spinal cord showing areas of demyelination, sclerosis and vascular thickening and sclerotic changes. The normal myelinated fibres are stained black. Note the superficial resemblance of the condition in this Fig. and in Figs. 747–8 on pp. 1158–60, illustrating subacute combined degeneration. Weigert-Pal's method. (× 7.)

In the areas supplied by these diseased vessels, local or widespread degenerative changes supervene, slowly or rapidly according to the nature and extent of the vascular involvement. One of the most important consequences of such arteritis is **thrombosis** (pp. 161 and 167) with its attendant results, including cerebral softening: or, in the case of the spinal cord, myelomalacia, with destruction of nerve-cells and fibres of perhaps several segments of the cord, most frequently in the thoracic region.

Syphilitic lesions of the spinal cord are analogous to those seen in the brain. There may, as noted in the preceding paragraphs, be thickening of all the **membranes,** with involvement of the nerve-roots, and, usually, associated myelitis (meningo-myelitis). **Syphilitic arteritis** is always a pronounced feature. **Gummata** develop from the inner surface of the dura, or from the pia-arachnoid, and cause pressure upon, and softening of, the cord. Sometimes, but more rarely, gummata are found in the substance of the cord. Degenerations caused by syphilis in the conducting tracts are described below.

The Cerebrospinal Fluid in Meningo-Vascular Syphilis. The investigation of cerebrospinal fluid in neurosyphilis is of importance for diagnosis, prognosis and treatment ; and the findings vary greatly in degree according to the stage of the disease, its acuteness or chronicity, the severity of the infection, and the treatment which has been adopted for it.

In the **late primary** and the **secondary** stages, abnormalities in the fluid may already be present in the form of slight or moderate mononuclear pleocytosis and perhaps also some increase in the protein-content and a change in the Lange colloidal-gold curve (p. 964). The Wassermann reaction usually becomes positive in the fluid only after it has become positive in the blood, although, as stated on p. 1004, its appearance in the fluid first has occasionally been recorded. If the disease has not been modified or arrested by treatment, a positive Wassermann reaction may be expected in the fluid in about a quarter to a third of patients with secondary rashes : and in the majority of late secondary cases, along with a more pronounced pleocytosis and an increase in globulin as well as in total protein. Stated generally, and in another way, about a quarter to a third of all patients infected with syphilis are likely to show abnormalities in the fluid during the first six months : and a third to about half of the cases in the course of the second six months—these results, naturally, being modified by early and efficient treatment.

In the **tertiary** stage, it has been observed that, as noted on p. 1002, neurosyphilitic manifestations tend to supervene particularly in patients in whom, during the primary and secondary stages, the symptoms have been mild, as well as in insufficiently-treated patients. It is in these cases that the information—positive or negative—obtained from the examination of the cerebrospinal fluid is essential for observation of the progress of the disease and the control of its further treatment. If the findings in the fluid, as well as in the blood, of patients who have received early and adequate treatment, are negative at five or six months and at two years after infection, it is unlikely that the case will develop neurosyphilis at a later date. It is well, however, as an additional precaution, to repeat these examinations at the end of three years. It is also important to realise that the reaction in the blood is no guide as to what will be found in the cerebrospinal fluid, which should itself, therefore, be re-examined, say, every four to six months in all clinically suspicious cases.[1]

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[1] This is a matter of such importance that we quote in full the following paragraph from Merritt and Fremont Smith's authoritative book (*loc. cit.*, pp. 115–116) :—

"**When should a Patient with Syphilis have a Lumbar Puncture?**"—"Every patient with syphilis should have one or more complete examinations of the cerebrospinal fluid. In a patient receiving treatment for early syphilis Moore (1933) recommends that lumbar punctures be performed about five and twenty-four months after the infection and states that if the cerebrospinal fluid is entirely normal on both these examinations further punctures are not necessary. This ideal cannot always be obtained, but no patient with syphilis should be discharged from treatment without an examination of the cerebrospinal fluid, even though the blood serology is consistently negative. A lumbar puncture should be performed as soon as possible in cases of late syphilis with tertiary manifestations or positive blood serology without any clinical evidence of neurosyphilis. A knowledge of the cerebrospinal fluid findings in such cases is of paramount importance in determining the type of therapy necessary. In cases with clinical evidence of neurosyphilis the cerebrospinal fluid findings should be checked at four- to six-month intervals to determine the effect of the therapy on the abnormalities."

In **meningo-vascular** or **cerebrospinal syphilis,** the Wassermann reaction in the fluid becomes almost uniformly positive, and is accompanied by a pleocytosis of 20 or 30 up to perhaps several hundred cells, mostly small, with moderate numbers of slightly larger, monocytes, often accompanied by a few polymorphonuclears, and associated with an increase of total protein of 50 to 150 mgr. per cent., a slight to moderate increase of globulin, and either a first-zone (paretic) or mid-zone (luetic) Lange-curve (p. 964). As noted on p. 1006, the formation of adhesions in the spinal subarachnoid space may lead to the occurrence of " spinal block " and the associated characteristic changes in the cerebrospinal fluid (p. 963). During the earlier stages in the formation of adhesions, fibroblasts may be found in the fluid microscopically (Fig. 579, p. 962). In severer cases of **acute syphilitic meningitis,** the various findings are more pronounced, *e.g.*, a pleocytosis of several hundred up to perhaps even a thousand cells or more.

A point of some importance which we have ourselves noted in the extensive series of routine examinations of the blood and cerebrospinal fluid carried out in the West End Hospital for Nervous Diseases, London, is that, in a not inconsiderable proportion of old infections, untreated, partially treated, or even apparently thoroughly treated, **a positive Meinicke clarification reaction may persist in varying degree in the blood** long after the Wassermann reaction has become negative in the blood and both W.R. and M.K.R. have become negative in the cerebrospinal fluid.

The characters of the cerebrospinal fluid in **general paresis** and **tabes dorsalis** are described under these varieties of syphilitic disease on pp. 1016 and 1019.

In the majority of cases of syphilis in its various stages, the amounts of sugar and chlorides in the cerebrospinal fluid are within normal limits.

(B) PARENCHYMATOUS NEUROSYPHILIS[1]

Why in some patients the spirochæte should attack the **parenchyma**[2] of the nervous system, *i.e.*, the nervous tissues themselves, whilst in others the infection is more or less restricted to the mesoblastic supporting tissue and vessels, is not understood. Some writers postulate the existence of special " neurotropic " strains of the organism, basing the suggestion upon the observation that, in certain instances, the parenchymatous form of the disease is believed to have ensued in a number of persons infected from the same source. Others explain the phenomenon as due to special instability of the central nervous system of certain susceptible individuals ; and it has also been thought that the particular route of infection may have some bearing on the problem, for example that in tabes dorsalis the spirochæte reaches the dorsal root-ganglia after lying latent in the mediastinal or abdominal lymph-nodes. It is difficult, however, on this hypothesis to explain the occasional involvement of the corresponding sensory ganglia on certain of the cranial nerves, seen in some cases of parenchymatous syphilis. Again, on the analogy of the neurotropic viral infections (pp. 97–8 and 105–6), it has been suggested that the spirochæte may reach the central nervous system directly by way of the nerves and nerve-trunks or by the lymphatics of these. It is also to be noted that, in a considerable proportion of post-mortems on cases of both general paresis and tabes dorsalis, syphilitic aortitis is found—the walls of the larger blood-vessels being among the sites in which the spirochæte tends to remain "latent" for long periods (p. 479 *et seq.*). The possible influence of some co-existing **vitamin-deficiency** (p. 441), more especially in the causation of tabes dorsalis, is referred to on p. 1016 (*cf.* pp. 1047, 1076–8, and 1160).

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[1] Previous to the realisation that **general paresis** and **tabes dorsalis**, though tending to supervene late in the course of the disease, are *direct* manifestations of infection with *Treponema pallidum*, these forms of the disease were described as " *para*syphilitic," *i.e.*, indirect manifestations of syphilis, or as " *meta*syphilis," implying a general degenerative condition following upon syphilis. As they are in reality definitely syphilitic lesions produced by the spirochæte, these terms should now be discarded. Similarly the term " General Paralysis of the Insane " was originally used because it was thought that insane persons were liable to develop the disease, whereas the mental deterioration is itself the direct result of the invasion of the central nervous system by the spirochæte and the changes there produced by it. As actual paralysis does not necessarily supervene until later, this manifestation of syphilis is therefore more suitably called " General Paresis," although in sufficiently advanced cases the older term " General Paralysis " may still be appropriate.

[2] " *Parénchўma,*" παρέγχῠμα, " anything poured into," hence " contents," a name given by Erasistratus (a famous Alexandrian physician and anatomist of the third century B.C.) for " the peculiar substance of an organ," as contrasted with the word *σάρξ*, *sarx*, pl. *σάρκες*, *sarkes*, used for " the muscular flesh," from which the word " sarcoma " is derived.

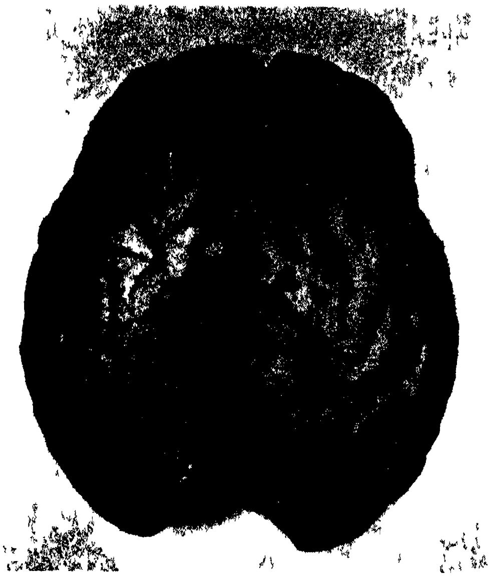


FIG. 609. *General paresis* (*dementia paralytica*). Brain (weighing 1,350 grammes) of a man aged thirty-seven, showing wasting of the gyri of especially the frontal and parietal lobes, with thickening of pia-arachnoid over vertex. Prior to fixation, the leptomeninx could not be stripped off the underlying brain-substance without damage to both. Wassermann reaction in blood and cerebrospinal fluid strongly positive : total protein 80 mgr. per 100 c.cm., with moderate excess of globulin : Lange's colloidal-gold curve 5555442100. (Dr. McMenemey's case.)

GENERAL PARESIS (*syn.* **General Paralysis of the Insane, "G.P.I."** or **Dementia Paralytica**) accounts for just under 10 per cent. of cases of neurosyphilis, its onset being usually from ten to fifteen years after the primary infection, though it is found sometimes as early as three or as late as thirty years afterwards. Males are attacked more frequently than females in the proportion of about four to one, the commonest age-incidence being between forty and fifty years. As noted in a subsequent section (pp. 1020–1), occasional cases of **juvenile** parenchymatous syphilis, paretic or tabetic, are a recognised occurrence in congenital infection, *e.g.*, in the second decade of life. Before the introduction of malarial treatment, along with which may now be included electric pyrotherapy, and the combination of this with the administration of bismuth and arsenic, now sometimes referred to as "chemothermy," the prognosis in general paresis was uniformly fatal, usually within a period of three years.

During the earlier or more acute period, the brain is swollen ; and hyperæmia and multiple foci of small round-celled infiltration and capillary hæmorrhages are observed. Brownish staining on the under or deep surface of the dura and perhaps the presence of a " pseudo-membrane " may point to previous subdural hæmorrhage (p. 974 *et seq.*). By the time death supervenes, however, most cases have reached the chronic stage (Fig. 609) in which there is degeneration and atrophy of the brain-substance, especially of the frontal (particularly their orbital surfaces) or frontal and parietal lobes, with shrinking of the convolutions and consequent opening-up and exaggeration of the intervening sulci. In the latter, there is compensatory or complementary accumulation of fluid in the meshes of the pia-arachnoid (p. 966), which also shows milky thickening, especially along the lines of the larger veins, tending to obscure the widened sulci. The smaller vessels of the leptomeninges are increased in number and tortuosity. The thickened pia is more adherent than normal to the subjacent brain-tissue, and, on attempting to strip it from the surface of the brain, small portions of the latter may tear away along with it. The Pacchionian bodies (*i.e.*, the arachnoidal villi large enough to be easily visible to the naked eye) are increased in size and number. Owing to the shrinkage of the brain as a whole, affecting both cortex and white matter, the ventricles gradually become dilated, usually in moderate degree, and a complementary or compensatory internal as well as external hydrocephalus is thus produced; and the walls of the dilated ventricles often show a roughening or granularity due to nodular subependymal glial proliferation.

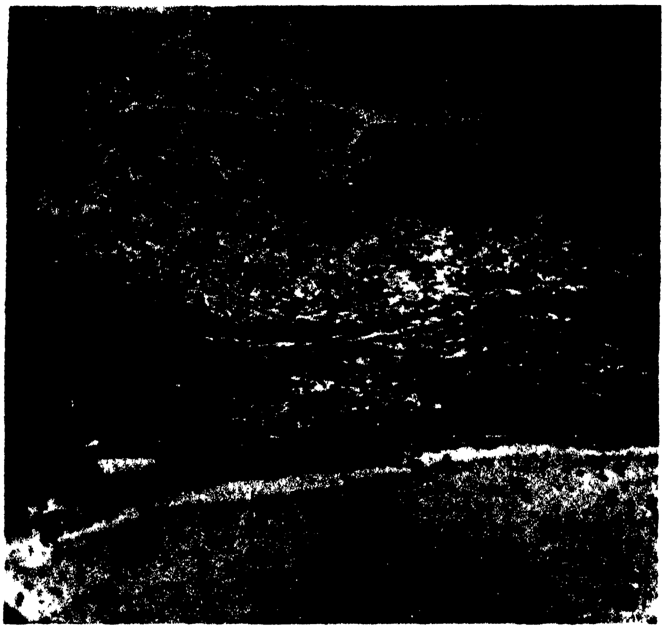


FIG. 610. *General paresis.* Vertical section through surface of a frontal convolution and the overlying leptomeninges, showing small round-celled infiltration and thickening of the pia-arachnoid. Hæmatoxylin and eosin. × 50.

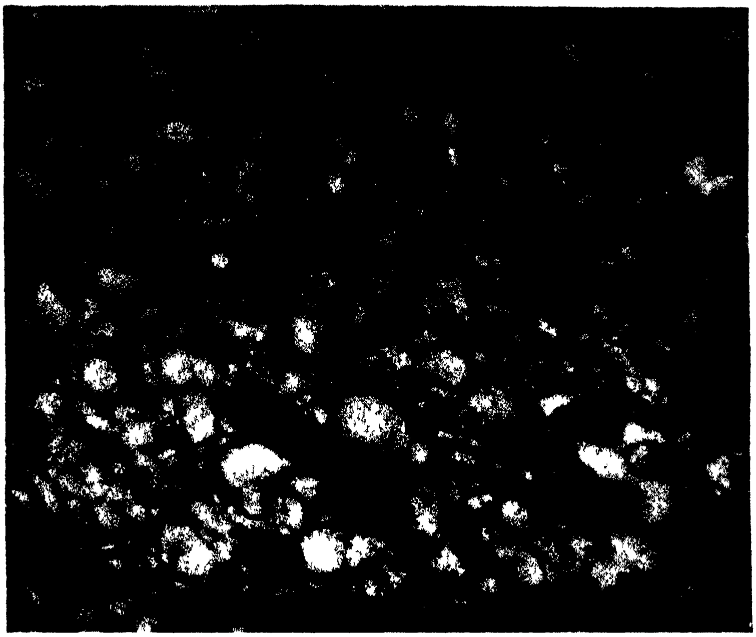


FIG. 611. *General paresis : Treponema pallidum* in the cerebral cortex. An untouched photograph showing several spirochætes impregnated by Jahnel's silver-nitrate method. × 950.

FIG. 612. *General paresis*. low-power view of vertical section through *frontal cortex* showing diffuse gliosis with increase of astrocytes and some thickening of the small vessels. At the upper left corner a small part of the surface does not yet show any pronounced gliosis of the glial element of the pia-glial membrane. Cajal's gold-sublimate method. × 80.

Although the brain-tissue is firmer than normal, the organ as a whole has thus somewhat the feeling of a bag with thick elastic walls.

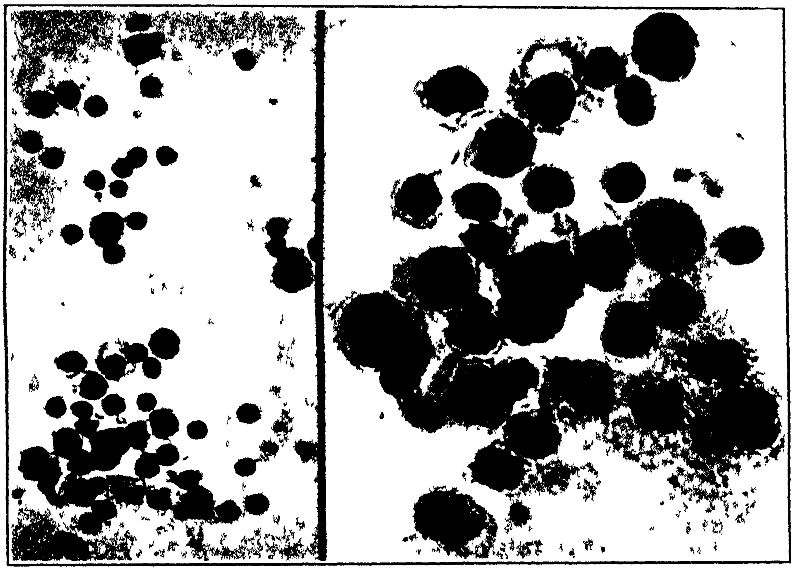
Microscopically, spirochætes are demonstrable in a considerable proportion of cases—in some series, it is said, in as many as 40 or 50 per cent.—most readily in the frontal lobes, basal ganglia and cerebellum—in which they are found not infrequently within the nerve-cells themselves. In early, and especially in acute, cases they are found sometimes in large numbers—occasionally even in so-called " swarms." In chronic and old-standing cases, however, the examination for spirochætes often yields negative results. The nerve-cells undergo progressive degeneration, perhaps in a patchy and irregular manner, particularly the cells of the molecular layer and the small and medium-sized pyramidal cells of the cortex. The degenerative changes are of the usual type—eccentricity of the nucleus, disappearance of the Nissl-granules, atrophy and finally disintegration of the whole nerve-cell, a process hastened by invasion and phagocytosis of the nerve-cells (" neuronophagy ") by microglial and other cells (*cf.* pp. 1118 and 1192). Where such degenerative and destructive processes have been in progress, the brain-tissue shows a patchy or diffuse opening-up of its meshwork—the so-called " status spongiosus." Demyelination, degeneration and disappearance of the corresponding axons follow the destruction of the nerve-cells, together with general glial proliferation, especially beneath the thickened pia-glial membrane and in the subependymal tissues, but also more or less generally throughout the brain. The astrocytes and microglia-cells are the elements chiefly involved, the oligodendrocytes much less so. The microglia-cells come to contain considerable quantities of **iron,** and a positive reaction for hæmosiderin in the affected cortex (the **Spatz-reaction**) is a point of diagnostic value. This phagocyted waste iron is derived apparently from the

FIG. 613. *General paresis:* frozen section of cerebral cortex impregnated with Hortega's silver-carbonate method to demonstrate the branching and rod-shaped *microglial cells,* which are increased in number. × 300.

breaking-down nerve-cells and not from hæmoglobin. It is found particularly in the cortex, and also in the basal ganglia, especially the pallidum, where it has been mistaken for calcification. Whilst demyelination is in progress, the microglia-cells come to contain much lipoid material, *i.e.*, develop into "foam-cells," "compound granular corpuscles" or "myelophages" (p. 956).

The meninges, as might be expected (for a general account of the lesions characteristic of syphilis *see* pp. 80 to 88 : 479 to 481 : and 1003 *et seq.*), show diffuse infiltration with small lymphocyte-like cells and plasma-cells, along with endo- and peri-arteritis, or perhaps a panarteritis, of their vessels, followed later by fibrosis.

Varying degrees of involvement of the vessels of the substance of the brain are found, sometimes slight in earlier stages, often pronounced, with perivascular cuffing, particularly with plasma-cells, as well as with small lymphocytes and microglial cells in varying proportions. There is not infrequently an actual proliferation of the smaller vessels in the affected areas of the cortex, with the formation of new capillaries. All these changes are best seen in the cerebral cortex, *e.g.*, of the frontal lobes, but are found also in the basal ganglia, pons and medulla, and, especially in congenital cases, in the cerebellum (Fig. 617, p. 1020).



(A) × 500. (B) × 1,250

FIG. 614. *General paresis cerebrospinal exudate* from a male patient aged forty-nine years, showing numerous small lymphocyte-like cells, as well as a considerable proportion of medium-sized and small endothelial cells from which they appear to be derived (*cf.* the analogous phenomena in acute cerebrospinal exudates illustrated on pp. 961 and 985–7). An occasional polymorph is also present. The Wassermann reaction was strongly positive, and the colloidal-gold curve 5555421000. (Fresh-wet film of centrifugalised deposit in toluidin blue.)

When death occurs during or after treatment of cases of general paresis by **artificial malarial infection,** various irritative and inflammatory reactions may be found in the brain and cord, as well as throughout the general reticulo-endothelial system of the body. The action of the malarial parasites on the red corpuscles leads to their destruction in large numbers, with the consequent discharge of their contents, which can then produce therapeutic and sometimes considerable toxic effects analogous to those of protein-shock (p. 135 *et seq.*). There is, at first, an intensification of the perivascular cellular reaction and infiltration in the meninges and nervous tissue ; but, later, these subside and become progressively less and less in evidence, the iron-containing microglia-cells also disappearing. The glial proliferation persists, and, as is to be expected, there is no regeneration of the damaged nerve-cells themselves.

The Cerebrospinal Fluid. In general paresis, the Wassermann reaction in the fluid is practically always positive, accompanied by a pleocytosis of up to 100 or more cells per cmm., mostly small lymphocytes with moderate numbers of small to medium-sized mononuclear (endothelial) cells, plasma-cells and, especially in the severer cases, a few polymorphs. The total protein may increase to 50 or 100 mgr. per 100 c.cm., the globulin especially being often increased, and the fluid giving the typical first-zone (paretic) colloidal-gold curve (p. 964).

TABES DORSALIS[1] or **Locomotor Ataxia** or **Ataxy.**[2] This disease is characterised clinically by the occurrence of " lancinating " or " lightning-pains," the loss of certain reflexes, ataxia or inco-ordination of muscular action, and various disturbances of sensation. It is unnecessary to discuss whether tabes is or is not of syphilitic origin, as it is now recognised as a form of neurosyphilis, although it is still an undecided problem *why* the dorsal nerve-roots and their ganglia should be specially picked out for attack by the spirochæte (p. 1010 *et seq.*). On the analogy of their experimental results with rats kept on a diet deficient in vitamin E, Einarson and Ringsted[3] (1938) have suggested that, not only certain muscular dystrophies and amyotrophic lateral sclerosis may, in whole or in part, be produced by **a deficiency of vitamin E** (p. 441), but that tabes dorsalis may similarly be brought about in syphilitic patients who are predisposed by such avitaminosis to the occurrence of degenerative changes in their spinal cords. On this hypothesis, and although, as might be expected from the nature of the permanent damage already done to the cord, his results in *advanced* cases of tabes were unsuccessful, Franklin Bicknell[3] believes that, if instituted sufficiently *early*, treatment of tabetic cases with vitamin E may be of value, because in the other diseases mentioned above he obtained definite clinical improvement with this form of therapy, although the prognosis in these conditions has hitherto been regarded as hopeless. An analogy certainly does exist between tabes dorsalis and " subacute combined sclerosis " as regards the nature and characteristic distribution of their lesions (Fig. 748, p. 1160), the latter disease being a degenerative condition almost certainly brought about by " deficiency " factors (p. 1157 *et seq.*).

The average period that elapses between the primary infection and the clinical onset of tabes dorsalis is about ten years, though in individual cases it varies from three up to twenty years or more. Its maximum incidence is between the ages of thirty-five and fifty years and the disease occurs in males oftener than females in the ratio of about nine to one. Although in the great majority of instances tabes supervenes upon an acquired infection, it also occurs occasionally, as does general paresis, in the course of congenital syphilis, as "**juvenile tabes**" (pp. 1020–21). Intermediate or combined forms of tabes and general paresis, known as **tabo-paresis,** though relatively uncommon, are found in patients suffering from either the congenital or the acquired variety of infection. It is sometimes difficult in cases of tabes dorsalis to elicit any definite history of a primary infection, and it has been noted that, as in general paresis, the clinical manifestations during the secondary stage of the disease may have been so slight as to have escaped notice. Because of this it has been suggested that neurosyphilis is less likely to follow when there have been pronounced cutaneous and other tissue-reactions, and therefore presumably a more active fight on the part of the tissues to produce immunity, such cases being also more likely to have been treated. In both of these forms of parenchymatous neurosyphilis—general paresis and tabes dorsalis—the response to any form of treatment is poor. The onset of symptoms indicating involvement of the central nervous system appears sometimes to be precipitated by an accident or intercurrent illness, though it is not unlikely that these have served merely to call attention to an ataxia already present.

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[1] Latin *tabes*, wasting (originally of the body generally, *i.e.*, emaciation), from *tabescĕre*, to waste away, but here now employed to denote the atrophy of the dorsal columns of the spinal cord. (*Cf.* the German, Rückenmarksschwindsucht.)

[2] Greek *ἀταξία*, *ataxia*, want of *τάξις*, *taxis*, order, from *τάσσειν*, *tassein*, to arrange—hence confusion, lack of co-ordination.

[3] L. Einarson and A. Ringsted, " Effect of Chronic Vitamin E Deficiency on the Nervous System and Skeletal Musculature in Adult Rats," 1938, Copenhagen. (Quoted by Franklin Bicknell, London, in his paper on " Vitamin E in the Treatment of Muscular Dystrophies and Nervous Diseases," *Lancet*, 1940, i, 10-13, *q.v.*)

On examining the spinal cord from a typical case *post mortem*, it shows wasting—" tabes "—of the posterior or dorsal columns, dorsal nerve-roots and root-ganglia, these—especially the dorsal columns—having a greyish translucent appearance and firmer consistence than normal.

Tabes dorsalis is essentially a syphilitic degenerative process attacking the sensory nerves, especially their trophic nerve-cells in the ganglia on the dorsal nerve-roots, the lesion in the cord itself being predominantly an ascending degeneration. The neurone-bodies lying in the dorsal root-ganglia show swelling, chromatolysis, vacuolation, pigmentation and sometimes fatty degeneration, at all events in advanced cases. The degeneration in the dorsal columns affects the exogenous fibres which enter from the dorsal roots ; whilst the endogenous association-fibres, *i.e.*, those which arise from cells of the grey matter within the cord itself and connect the various segments with one another, and which lie mainly at the anterior or ventral part of the dorsal columns, just behind the grey commissure, are *not* affected in lesions of the dorsal nerve-roots, and they therefore escape in typical tabes dorsalis. These facts demonstrate that tabes is a disease of the sensory neurones, and not a primary disease of the spinal cord itself.

In the cord, the changes are most pronounced in the **dorsal columns,** especially in the **lumbar** or **lumbo-thoracic** region ; but, in rare cases, the cervical region is the part of the cord attacked—"**cervical tabes.**" The spinal cord may be smaller in diameter than normal, and the pia thickened and adherent, perhaps irregularly, over small areas on the posterior surface. The **dorsal nerve-roots** are diminished in size, their **ganglia** showing the degenerative changes described below. In other instances, the dura, pia, and dorsal nerve-roots show comparatively little alteration to the naked eye, although microscopic changes may be found.

In early cases, the disease attacks the postero-lateral tract (or marginal zone of Lissauer) and those parts of the funiculus cuneatus (or dorso-external tract of Burdach) which adjoin the dorsal horns. In relation to this distribution it should be noted that some of the fibres from the dorsal or posterior nerve-roots enter opposite the apex of the dorsal horn of grey matter and turn upwards in the postero-lateral zone of Lissauer. Some then enter the dorso-external tract, their position being first at its outer margin, and then gradually shifting inwards as they ascend, being displaced towards the middle line by successive waves of incoming fibres from each dorsal root, until in the upper reaches of the cord they continue to ascend as the funiculus gracilis (dorso-internal or dorso-mesial tract of Goll) to reach the nucleus gracilis in the medulla. Some enter the dorsal grey matter (of the posterior horn) at a higher level, whilst others turn downwards in the semilunar (or comma) tract. The disease begins, in the majority of cases, in the nerve-cells of the dorsal ganglia of the lumbar nerves, and therefore in the early stages the fibres derived from these are principally affected ; but, as the condition advances, a larger number of ganglia are involved and a greater extent of tissue becomes degenerated in the dorsal columns. The written description of this process makes it appear complicated, but reference to appropriate anatomical diagrams will render it fairly simple.[1] The degeneration in the dorsal nerve-roots may be traced to the spinal ganglia—the cells of which, as already noted, may be shrunken, may stain very deeply, and show vacuolation, and a high degree of pigmentation. In advanced cases, there may be destruction of all the cells in the affected ganglia. The immediate consequence of the destruction of these sensory

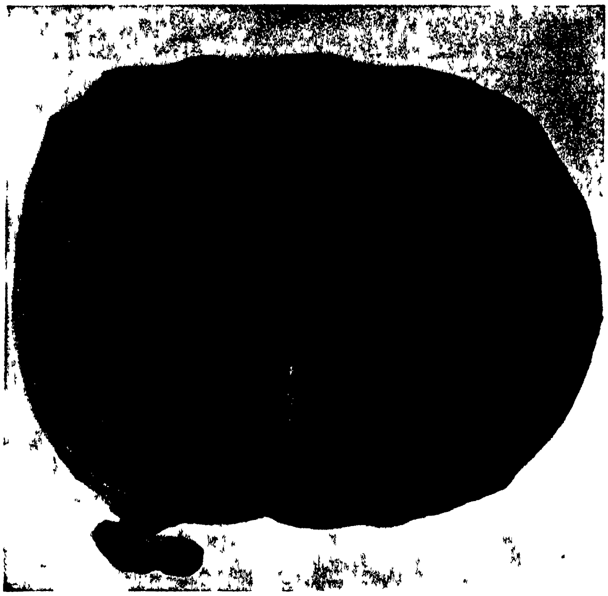

FIG. 615. *Tabes dorsalis* transverse section showing advanced sclerosis and atrophy, *i.e.*, " tabes," of the dorsal columns, together with chronic adhesions and thickening of the membranes. (Weigert Pal method for myelin. × 6.)

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[1] *E.g.*, Plate 45 of the Central Nervous System in E. B. Jamieson's " Illustrations of Anatomy," and Figs. 543 to 547 in Schafer's " Essentials of Histology," 14th ed., edited by H. M. Carleton, 1938.

nerve-cells is an ascending degeneration of the corresponding nerve-fibres affecting both the myelin-sheaths and axis-cylinder processes, the final result being their disappearance and replacement by dense glial proliferation, *i.e.*, a sclerosis, with thickening of vessels and leptomeninges. The changes in the peripheral, cranial, and sympathetic nerves are variable, but when present are all of a degenerative nature, the nerve-fibres being affected, and the connective tissue increased. It is, as might be expected, particularly the sensory nerves which are implicated, more especially the fine filaments supplying the skin and joints. The optic discs and nerves show primary atrophy in about 10 per cent. of cases ; or the atrophy may be secondary to a syphilitic interstitial neuritis. The ganglia and sensory fibres of the trigeminal and other cranial nerves are sometimes implicated. Loss of reflexes, *e.g.*, of the knee-jerks, is due to interruption of the sensory part of the sensori-motor reflex arc : loss of the contraction of the pupil to light, to interference with the oculo-sympathetic pupillo-dilator fibres, perhaps in the mid-brain in the region of the cerebral aqueduct. In the cord, the degenerative process in rare instances tends to spread transversely to the lateral columns, but frequently there is some degeneration in the dorsal horns of the cord, and, exceptionally, in the ventral horns. For a description of tabetic arthropathy (" Charcot's Joints "), *see* p. 1239.

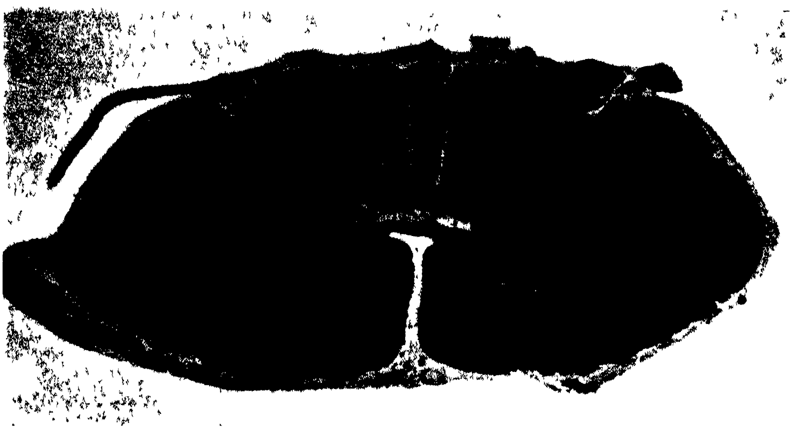
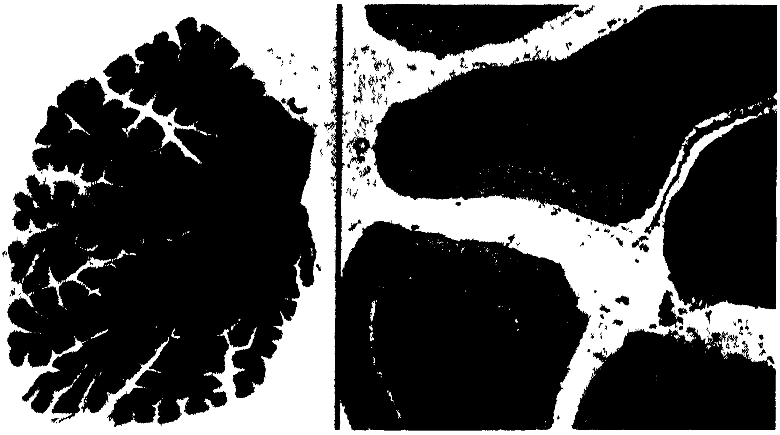


FIG. 616. *Tabes dorsalis :* transverse section of cervical region of spinal cord showing demyelination in dorsal columns. The relatively unaffected incoming fibres from the dorsal roots of the upper thoracic and lower cervical regions have taken up their position at the outer margin of the dorso-external tract on each side. Syphilitic leptomeningitis is also present. (Weigert-Pal method. × 7.)

The Cerebrospinal Fluid in Tabes Dorsalis. The Wassermann reaction is positive in both the blood and fluid in about 65 per cent. of cases : in the blood alone in about 5 per cent. : and in the cerebrospinal fluid alone in some 10 per cent. ; whilst the reaction may be negative in both in about 20 per cent. There is usually a moderate mononuclear pleocytosis of 5 to 75 cells or more, mostly small lymphocyte-like cells, perhaps with a few small endothelial cells, polymorphs being exceptional : with a moderate increase of total protein, and the excess of globulin being slight to moderate only, and associated with a mid-zone (luetic) colloidal-gold curve (p. 964).

Syphilitic spinal paraplegia or **Erb's progressive spastic paraplegia** is probably a form of syphilitic myelitis attacking the pyramidal tracts, but a similar clinical picture may follow involvement of these in subacute combined degeneration (p. 1157) and in disseminated sclerosis (p. 1059). It is probable that this group of conditions accounts for what at one time was called "primary lateral sclerosis."

CONGENITAL NEUROSYPHILIS. In different series of published cases of congenital syphilis, it has been stated that involvement of the nervous system takes place in from 5 up to 25 per cent. or more. Pathological changes are demonstrable in the cerebrospinal fluid in about 30 per cent. of these congenital cases during the first decade of life : in just under 20 per cent. in the second : and in 10 per cent. between the ages of twenty and thirty years ; after which, in patients who survive, the fluid usually ceases to show any of the abnormalities characteristic of active syphilis. Males are more liable than females ; and, except for the fact that the disease interferes with normal growth and development (see under general description of syphilis, pp. 83–86), the lesions in the nervous system are similar or analogous to those produced by the acquired form of the disease. In congenital syphilis, Hutchinson's triad of symptoms, deafness, interstitial keratitis, and malformed teeth (p. 83), are characteristic ; whilst other eye-lesions such as irido-cyclitis, choroido-retinitis and involvement of the optic nerves are not uncommon, as are also involvement of the facial, auditory and other cranial nerves. Varying degrees of hydrocephalus and many obscure proliferative sclerotic and other lesions in the brain often lead to mental deficiency. During the first decade, acute syphilitic meningitis, meningo-vascular infection and meningomyelitis occur ; and, in the second and third decades, dementia paralytica (" juvenile G.P.I.") and tabes dorsalis (" juvenile tabes"), and occasionally both of these in combination as "juvenile



(A) × 2½. (B) × 15

FIG. 617. *Cerebellum of a young child with congenital syphilis :* a patch of syphilitic encephalitis and degeneration affecting the cerebellar folia seen as the pale area (*a*) in the centre of the left margin of the left-hand figure (A), which is only very slightly magnified. Details are shown in the right-hand figure (B), with adjacent more normal folia below for comparison. (Dr. McMenemey's case.) (Mallory's phosphotungstic-acid hæmatoxylin method.)

taboparesis," are found. "Juvenile G.P.I." was first described by Clouston [1] of Edinburgh in 1877, under the title "developmental general paralysis." This juvenile variety of the disease is said to account for between 1 and 2 per cent. of all cases of general paresis. In it there is progressive mental deterioration, the patient becoming increasingly apathetic, with outbreaks of irritability and destructiveness; but delusions, *e.g.*, of "grandeur," so characteristic of the adult type, are not as a rule found in these juvenile patients.

In a considerable proportion of Wassermann examinations of the blood in the case of children, adolescents and young adults in whom congenital syphilitic infection is suspected, a "minimal positive result," such as the deviation of only 1 M.H.D. of complement, may be of significance, and even a delay in the rate of hæmolysis may help to confirm the suspected diagnosis in such cases, even when the Meinicke and Kahn reactions are negative. In patients in whom congenital neurosyphilis is suspected, however, a negative Wassermann reaction in the blood does *not* by any means exclude the possibility of that diagnosis. In some old infections, on the other hand, the M.K.R. may remain positive in the blood long after the W.R. has become negative in both blood and fluid (*see* p. 1010).

SECTION VI

OTHER PATHOLOGICAL CHANGES OCCURRING IN THE LEPTOMENINGES:

The results of certain non-fatal inflammatory lesions of the meninges have sometimes been described under the term "chronic arachnoiditis," but these are to be regarded rather as thickenings and adhesions occurring as the end-result of some previous irritative or inflammatory attack affecting the pia-arachnoid, or of vascular and other degenerative conditions. Local, or in some cases widespread, adhesions, occasionally leading to the formation of **encysted collections of cerebrospinal fluid,** are not very uncommon, especially on the surface of the spinal cord (Fig. 618, p. 1022). They may also be found over the convexity of the cerebral hemispheres or elsewhere, and they are not infrequently seen during operations in the neighbourhood of cerebello-pontine-angle tumours (p. 1140 and *cf.* Fig. 721, A, p. 1135). When situated over some part of the surface of the hemispheres, the condition has sometimes been described as "meningitis serosa circumscripta." If at the base of the brain, *e.g.*, in the interpeduncular space or its neighbourhood, compression of the optic chiasma may result. These encysted collections of fluid are in some cases contained within thin transparent walls which are easily ruptured at operation or post-mortem. A sudden gush of clear colourless cerebrospinal fluid occurs and the collapsed walls then become so inconspicuous as almost to escape further notice; yet such encysted collections of fluid can cause serious clinical symptoms, *e.g.*, compression-paraplegia with resulting ascending and descending tract-degenerations in the spinal cord, as in the case of the patient from whom the specimen illustrated in Fig. 618 was obtained. Where more widespread and diffuse, for example when due to or following birth-injury with subarachnoid hæmorrhage, or after some inflammatory condition leading to parasagittal adhesions and obliteration of arachnoid villi, an external communicating hydrocephalus may ensue (p. 968). There is nothing sufficiently specific about these lesions to justify the special term " arachnoiditis " being given to them. They are the end-results of trauma, subarachnoid hæmorrhage, or attacks of various non-fatal forms of meningitis, *e.g.*, meningococcal and " acute lymphocytic," as well as some varieties of syphilitic infection (including tabes dorsalis), disseminated sclerosis, and virus-produced " encephalitic " diseases ; and such adhesions and their results are not unlikely in the future to be found as a sequel in some of the cases of infection of the meninges due to *Streptococcus pyogenes*, pneumococci and other organisms, which have reacted favourably to treatment with one or other of the sulphanilamide drugs. The leptomeninges may in some instances exhibit little or no naked-eye thickening or opacity; in others they are in varying degree thickened and opaque, the resulting appearances depending largely upon the nature of the primary causal lesion and the period of time elapsing since its occurrence.

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[1] Sir Thomas (then Dr. T. S.) Clouston, "Clinical Lectures on Mental Diseases," 5th ed., 1898, p. 403, Churchill & Co., London: "I have lately seen several cases of what I have called '*developmental general paralysis*.' The disease is very rare before the age of twenty-five, but a few cases had been reported—one by myself in 1877 (in the author's '*Neuroses of Development*') —at ages from twelve to twenty." Clouston then goes on to describe two further cases, both in girls of fifteen suffering from hereditary syphilis—although he did not at that date stress the essentially syphilitic nature of the disease.

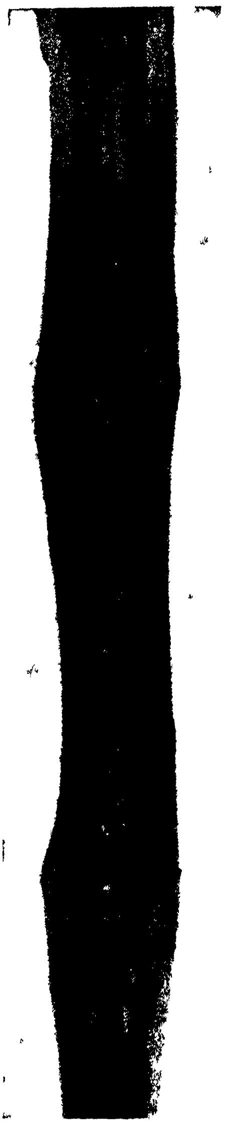

FIG. 618. *Thin-walled arachnoid cyst*, containing clear colourless fluid. It caused compression-paraplegia in a boy aged thirteen years, the clinical diagnosis having been " encephalo-myelitis." (W.E.H. case).

Hydrocephalus as a congenital abnormality is described on p. 968.

Increase in the bulk of the brain can occur without any apparent pathological alteration in the brain-substance. In other instances, however, this increase, sometimes described incorrectly as " hypertrophy," is associated with a hyperplasia of the neuroglial supporting tissue.

Atrophy of the Brain. In general cachectic diseases, the brain does not waste to the same extent or in the same proportion as other body-structures; but, in old people and in cases of presenile dementia (p. 1079), and also in alcoholics, some degree of atrophy of the convolutions takes place. A similar condition is seen in general paresis (p. 1011 *et seq.* and Fig. 609), especially in the frontal region, and also in cases where arterial degeneration is a prominent feature. The fluid in the meshes of the pia-arachnoid is correspondingly increased, and this increase is sometimes mistaken for dropsy. There may be slight or moderate dilatation of the lateral ventricles ; but, in some of the conditions of chronic diffuse encephalitis (p. 966), this **retraction-hydrocephalus,** due to the gradual shrinkage of the brain, may become progressively more pronounced. The pia is usually thickened and more adherent to the brain-substance than normal, and this thickening may be unilateral, or may appear as a general or as a patchy milky opacity, or in the form of irregular flattened whitish nodules. The perivascular Virchow-Robin spaces and also the perineuronal spaces may be dilated because of the atrophy and retraction of the surrounding brain-substance.

Local atrophy results from the pressure of tumours and aneurysms: or from loss of blood-supply, gradual in the case of slow degenerative narrowing of an artery, or rapid when following upon hæmorrhage, embolism, or thrombosis, with subsequent softening and absorption. In such cases, cavities or pseudocysts with a smooth lining and clear, or, if there has been hæmorrhage, yellowish or brownish serous, contents, may be formed; and there may also be, in the affected area, an abnormal distension of the Virchow-Robin perivascular spaces, which become filled with fluid.

INJURIES

Injuries to the brain may result from penetrating wounds of the skull, blows and crushing injuries of varying degrees of violence to the head, from the blast of explosives, from falls upon the buttocks, or from the sudden stoppage of vehicles. The injuries may vary from slight concussion up to immediately fatal complete crushing of the skull and its contents.

The force of a blow upon the head is transmitted from the point or area of impact and is modified by the structures through which it passes. Some temporary distortion of the skull at the moment of impact may be produced, with or without fracture, and the force is then transmitted to the subjacent contents. The brain from this point of view does not resemble a wet air-filled sponge or even a soft gelatinous mass which damps off the vibrations; but it and the blood in its vessels and the cerebrospinal fluid in its meshes and in the ventricular and arachnoid spaces constitute or are practically equivalent to a mass of incompressible fluid through which many of the vibrations are rapidly transmitted as through water. At the same time a mass-motion of the intracranial contents as a whole in the direction of a heavy blow is set up, and is as suddenly arrested against the opposite wall of the cavity of the skull, and also in varying and lesser degree at any intermediate points of resistance such as the tense edges of the horseshoe-shaped incisura of the tentorium cerebelli or of the falx. Bruising and damage to the brain is therefore liable to be produced (1) over its surface under the bone immediately beneath the site of the impact; (2) at the opposite side of the brain by so-called "*contre-coup*" (for example, at the temporal poles and frontal lobes, especially the under surfaces of the latter, if the blow has been to the back of the head); (3) in the brain-stem, etc., against the incisura (p. 1041); and (4) more general or, it may be, scattered or sometimes localised damage from the "concussion" or "commotion" may be caused by the short, sharp and rapid vibrations transmitted through the whole intracranial "incompressible-fluid" system. These concussing vibrations act particularly upon the delicate and important autonomic nervous structures of the hypothalamus around the third ventricle, leading to the production of the group of symptoms specially characteristic of concussion, viz., **unconsciousness, retrograde amnesia,** with headache and perhaps vomiting. Van Valkenburg[1] of Amsterdam (1940), describes the occurrence of a **polymorphonuclear leucocytosis** of 10,000 to 30,000 per c.mm., disappearance of eosinophils from the peripheral circulation, together with what he regards as almost pathognomonic of concussion when found along with the foregoing symptoms—a **lymphopenia** of under 1,500 lymphocytes per c.mm., or, in the case of children, a fall of lymphocytes to from 10 to 20 per cent. of the total leucocytes present. This lymphopenia he finds during the first twenty-four hours, or perhaps for three or four days, after the injury, then passing off as the eosinophils reappear and the total count returns to normal.

The damage thus produced may be highly complex in its character and distribution. The attempt is sometimes made to distinguish between "**concussion**"—defined as "traumatic unconsciousness"—and "**contusion,**" as being conditions in which there are respectively "no ascertainable lesions" and, on the other hand. "definite bruising" of brain-tissue. This attempted differentiation is, however, theoretical rather than practical, as in individual cases all intermediate variations and admixtures of the two conditions can occur simultaneously. Moreover, many pathologists would regard the symptoms of "concussion" as the result of certain finer, but yet in many instances demonstrable, changes in the nervous tissues, and, particularly in the more serious cases, followed, it may be, by degenerative sequelæ especially in the damaged neurones and their nerve-fibres, as well as by an accompanying œdema. It might of course be said that the presence even of these finer lesions would, by definition, bring the case into the category of "contusion," and that "cases of pure concussion do not die," but this differentiation is, in our opinion and from a pathological point of view, neither practical nor practicable.

Fracture of the skull is a subject described in surgical textbooks. Injuries to the **meninges and their blood-vessels** are discussed on p. 974 *et seq.* The lesions produced in the **brain and cord** may affect vessels, nerve-cells and nerve-fibres. Glial changes, however, though to a variable extent immediate and due to the bruising and damage caused at the time of injury, may be secondary to the occurrence of hæmorrhage or œdema, but are mostly of the nature of subsequent proliferation and formation of scar-tissue. **Contusion** or bruising, whether produced directly at the immediate site of impact or indirectly by *contre-coup,* may be accompanied by hæmorrhage and followed by œdema. Such œdema may be local or widespread, with separation and distension and perhaps some tearing of the glial meshwork, and a varying amount of damage to nerve-fibres, with rupture, it may be, of some fibres, and subsequent demyelination, partial or complete, of others, together with degenerative changes in the nerve-cells. These lesions are often patchy and localised in distribution, and are most pronounced in and around the areas of contusion or hæmorrhage. In the damaged areas, phagocytic microglial cells often rapidly collect, even within a few hours of the injury, and in a few days are found in the form of "foam-cells" laden with the fatty debris of disintegrating myelin and of hæmorrhagic and necrotic material. Mott described a general chromatolytic change in the nerve-cells of the central nervous system following upon such accidents—those most affected being the small cells in which the basiphil substance has partly or wholly disappeared; whilst in the larger nerve-cells the Nissl-granules are diminished in size and number. Others have found these nerve-cell changes less widespread, affecting perhaps some cells, whilst others in the immediate neighbourhood have escaped. Small depressed cup-like surface indentations, sometimes surrounded by little rings of hæmorrhage at their periphery, are not infrequently found over the summits of damaged convolutions as a sequel of such injuries, leading later to the production of irregular depressed glial scars. In the substance of the brain, small pseudocystic cavities—so-called "traumatic cysts"—sometimes result from the absorption of hæmorrhagic or necrotic areas. These show walls of proliferated glia, mixed perhaps with brownish blood-pigment. Patchy, or even extensive, areas of diffuse gliosis are a sequel, especially in severe cases, leading to shrinkage of brain-tissue and even to distortion of the ventricles sufficient in degree to be diagnosed by ventriculography. Traces of blood may find their way into the cerebrospinal fluid in the ventricles; or even considerable hæmorrhage into these, including the fourth ventricle, from their damaged walls, may be a serious complication of head-accidents; and, on lumbar puncture, the cerebrospinal fluid may be blood-stained (p. 958 *et seq.*). Macroscopic hæmorrhages into the important structures in the floor of the fourth ventricle or around the cerebral aqueduct were found in 25 out of 42 cases of fatal head-injury examined specially for these by Berner in Oslo between the years 1930 and 1932.

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[1] "The Concussional and Post-Concussional Syndromes," by C. T. van Valkenburg, *Lancet,* 1904, i, 1003.

The assumption sometimes made that the cerebral cortex or neopallium is the chief seat of consciousness in the brain is not borne out by the study of the effects of these and analogous lesions, and such study seems to suggest that the unconsciousness occurring in cases of accident and injury is due to the effects of the concussion upon the region of the "ancient" or more primitive optic thalamus and its connections; whilst involvement of the equally primitive hypothalamus probably accounts for the transient rise in blood-sugar and the occasional occurrence of glycosuria, as well as for the emotional and other disturbances of the vegetative functions and metabolism seen not infrequently as a result of "concussion."

In cases of **fracture of the skull,** the prognosis depends, not only upon the site, and on the nature and extent of the immediate injury and the occurrence of hæmorrhage, but also upon the presence or absence of any **septic infection** introduced either at the time of the accident or later. This is equally true of **penetrating wounds,** *e.g.*, those due to bullets or fragments of shell. Clean wounds of brain-tissue heal rapidly, whereas septic wounds may produce considerable areas of suppuration and perhaps meningitis. In such cases, a condition of "**latent sepsis**" may occur, and wounds which penetrate deeply into the brain may, after a relatively long period of apparent quiescence, be followed by encephalitis, abscess-formation or meningitis, these exacerbations being induced, it may be, by some subsequent and perhaps apparently trivial accident or by an attack of intercurrent disease.

Injuries and Accidents to the Spinal Cord.[1] The spinal cord is to a large extent more securely protected against injury than is the brain. The cord is much narrower than the vertebral canal in which it lies, and its membranes are separated from the walls of the canal by a considerable space. The cord may, however, suffer various degrees of damage from concussion and contusion produced by a severe blow on the neck or back: or from stretching and even laceration and tearing, nipping or complete rupture brought about by forcible bending or sudden deformation of the vertebral column, with or without fracture or dislocation of any of the vertebræ.

As in the case of the brain, the results of such accidents may be of all degrees, from slight jarring or concussion up to complete destruction and disintegration of the damaged portion of the cord, the cervical region being most liable to injury. Such damage may consist of a few small petechial hæmorrhages up to extensive bleeding into or around the tissues of the cord from injuries to smaller or larger vessels : degenerative changes in nerve-cells, sometimes picking out certain of these whilst others near them escape : stretching and perhaps rupture of varying numbers of nerve-fibres, and demyelination, with the maximum at the site of injury, though degenerative changes may be found for a few segments above and below, accompanied by œdematous softening up to perhaps complete necrosis or myelomalacia.

Compression of the cord or of nerve-roots, *e.g.*, of the cauda equina, may also be brought about by **herniation of intervertebral disks** or by **fibrotic thickening of the ligamenta flava**, especially in the lumbar region, often with a history of some injury to the spine to account for the production of the original lesions (pp. 1220 and 1223).

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[1] A further reference to these, more especially in relation to aviation, will be found on pp. 1165–6.

SECTION VII

CIRCULATORY DISTURBANCES OF THE NEURAXIS

Acute congestion of the brain and spinal cord may be active or passive, and can be produced by any of the usual causes of these conditions (p. 148). The congestion may affect the surface meningeal vessels, the vessels of the brain-substance, or in many cases both of these. Amongst general causes, **respiratory embarrassment** produces a considerable degree of congestion, and is a pronounced feature in death from opium- and other forms of poisoning characterised by respiratory failure. Varying degrees of acute congestion, especially of surface vessels, follow upon obstruction of certain of the larger cerebral arteries, veins, or venous sinuses (Figs. 620–1, pp. 1030–1).

In cases of **encephalitis,** general or local (pp. 105 *et seq.* and 1047 *et seq.*), acute hyperæmia is found, not merely in the pial vessels over the surface, but also as a general pinkish tint of the substance of the brain or cord seen on section. It is usually more marked in the grey than in the white matter, and in its more intense forms may be accompanied by varying numbers of petechial or larger **hæmorrhages.** Over the cut surface of the congested hemispheres may be seen numerous small bleeding points, the so-called *puncta cruenta* or *vasculosa,* corresponding to the openings of severed small engorged veins, usually seen best in sections of the white matter. **General** acute congestion is present in the acute encephalitis of viral infections such as epidemic encephalitis (p. 109), and also in varying degree in cases of death from any of the acute infective fevers, septicæmias and similar diseases. As a **local** change it is found in or around acute inflammatory lesions, *e.g.*, abscess, meningococcal endoventriculitis (pp. 983–4) and other infections, and also not infrequently in the case of certain tumours, especially if malignant and rapidly growing, and if necrosis is present.

Chronic venous congestion, at all events as a post-mortem finding, is not usually a prominent feature in the brain, especially if, in the course of the examination, the chest and abdomen have been opened *before* the head, in which case the cerebral veins, even if previously engorged, may be emptied of blood. In cases of mitral disease, with extensive venous congestion in the lungs, liver, etc., the only evidence of the condition in the brain may be some distension and tortuosity of the vessels in the pia-mater, and a slight deposit of pigment round these vessels and the presence of *puncta cruenta* (see above) on the cut surface of the brain. Chronic congestion may result also from thrombosis of the sinuses or of the great cerebral vein of Galen, but, unless the thrombosis has spread also into the other cerebral veins, the appearances after death are often inconspicuous.

Œdema or **Dropsy** (p. 178 *et seq.*). Œdema of the brain-substance occurs in cases of nephritis and nephrosis where these are characterised by general " renal dropsy " : in cerebral thrombosis, arterial or venous : to a varying degree in acute inflammation of the brain-substance (encephalitis) : and also in and around areas of trauma. In cases of hydrocephalus (p. 966 *et seq.*), what may be described as " backward pressure " of the cerebrospinal fluid into the Virchow-Robin spaces may produce what practically amounts to œdematous distension of these around the blood-vessels. The affected brain becomes swollen, with consequent flattening of the surface convolutions against the interior of the skull. The grey matter normally contains about 83 to 85 per cent. of fluid, and is much less affected by the œdema than is the **white matter,** the normal liquid-content of which is about 70 per cent., an amount which may increase to 75 or perhaps 80 per cent. in an œdematous brain, in which there is likewise a notable increase of **sodium chloride,** which is present only in small amount in the normal brain, but which, in œdema, may come to equal that present in the blood-plasma. The brain-substance may be firmer, but is often softer, than normal, and, when cut across, usually but not invariably presents a pale, glistening, watery appearance, the fluid in the ventricles being also increased in amount, and the meshes of the pia-arachnoid containing excess of fluid. As already mentioned, these may be the only naked-eye evidence in certain cases, especially of renal disease, in which the clinical symptoms (*e.g.*, monoplegia, hemiplegia, etc.) may have suggested the presence of some more definitely localised cerebral lesion such as hæmorrhage or embolism.

Local œdema may be present in the neighbourhood of tumours, hæmorrhages or abscesses, and also in and around areas damaged by accident or injury. Collections of cerebrospinal fluid over the surface of degenerated and contracted areas of brain-tissue do *not* constitute true œdema, but are merely a replacement-phenomenon (pp. 966 and 1022).

Histologically, œdema shows—more particularly **in the white matter**—as a spongy distension of the glial meshwork and of the perivascular, and, in the grey matter, also of the perineuronal, spaces, constituting one form of the so-called " status spongiosus " ; and there is also a varying degree of swelling of the glial cells, chiefly of the astrocytes rather than of the oligodendrocytes, which are usually but little affected—and of the nerve-fibres and their myelin-sheaths. If the latter undergo any disintegration, there may be some mobilisation of the microglial cells as phagocytic " foam-cells " to clear up the debris (p. 956).

Deficient Blood-Supply. The technical term " anæmia " is best reserved for general conditions of the blood itself, although it is sometimes rather loosely applied to the condition of **ischæmia** or deficiency in the mechanical supply of blood to the brain, whether transitory, as in cardiac syncope (pp. 183–4), or persisting, as when due to lesions such as stenosis of the aortic valve. There may thus be interference with the efficient supply of blood to the brain from any of the numerous causes, general or local, described on pp. 147 *et seq.*, and 167 *et seq.* Though such deficiencies, qualitative or quantitative, in the supply of blood may be a cause of death, there are, except for general pallor of the organ, no characteristic post-mortem appearances in the brain.

Anoxæmia,[1] or an inadequate supply of oxygen to the tissues (p. 157), is of special importance when the tissues involved are those of the central nervous system. Transient anoxæmia may cause unconsciousness ; but, where more prolonged, the nerve-cells may suffer in varying degree, and any change, from slight degeneration up to complete necrosis, may follow. In the condition of **apnœa neonatorum** (still-birth), it is now thought that hæmorrhage from birth-injury is, in recent years at all events, a much less frequent and less important cause than is the depressive action of drugs such as hyoscine (scopolamine) and the barbiturates administered to the mother and acting **upon the respiratory centre** of the child.

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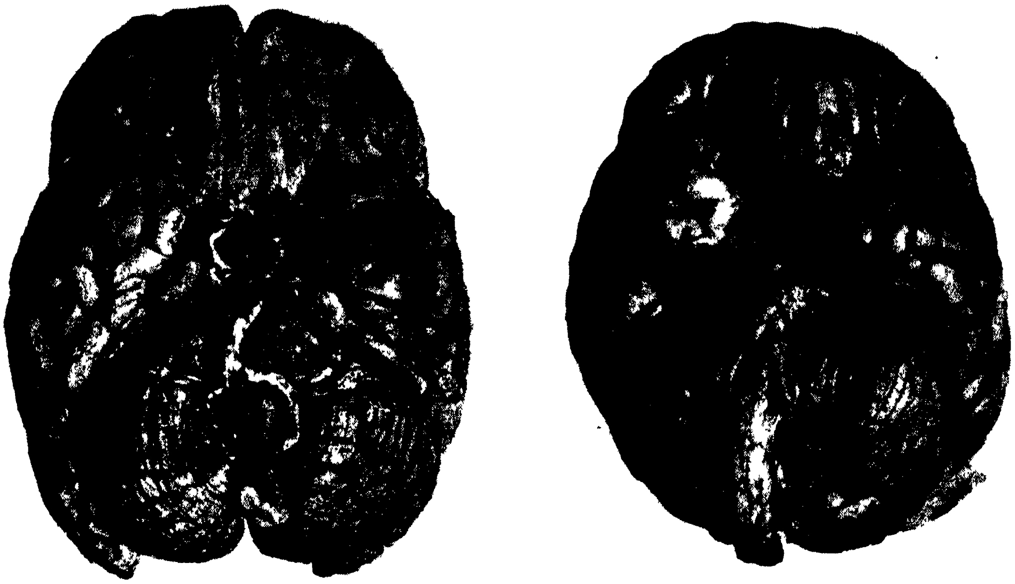
[1] *See* footnote, p. 157.

Local deficiency in blood-supply (**ischæmia**) may arise from local pressure produced by tumours, extravasations of blood, inflammatory exudates, etc., but the commonest and most important cause is obstruction of arteries.

Arterial Obstruction may be produced by **thrombosis** or by **embolism,** the general mechanism and results of which are described on pp. 161 and 168. For example, a portion of clot in a thrombosed pulmonary vein may become detached and pass through the left side of the heart into the aorta and be carried to the brain, and, if such clot is infected, the embolism may be followed by abscess-formation. In an analogous fashion, fragments of tumour or tumour-cells may be carried from lung to brain, this being probably the explanation why metastases are of such common occurrence in the brain in cases of primary bronchial carcinoma (pp. 569–576 and 1146 *et seq.*). Much less frequently, as explained on p. 171, in cases of patent foramen ovale or with a deficient interventricular septum, a fragment of thrombus formed in one of the systemic veins may be carried through the abnormal opening from the right to the left side of the heart and then reach the brain—the phenomenon known as **paradoxical** or **crossed embolism** (*see also under* "Retrograde Embolism," p. 171 *et seq.*). Again, in **fat-embolism** of the lung (p. 169), originating from the bone-marrow in fractures of, say, one of the long bones or



(A) (B)

FIG. 619. *Atheroma of cerebral arteries.*

(A) Brain of elderly male. Atheroma of vessels at base with tortuosity and irregular dilatation. The internal carotids and vertebrals on each side show great inequality in size.

(B) Brain of a man, aged fifty-two, showing extensive atheroma of cerebral vessels with thrombosis of left vertebral artery. (There was also an extensive terminal hæmorrhage in the right centrum ovale and ventricles following an injection of thorotrast (see Fig. 628, p. 1037), a procedure not without grave risk, especially in a patient with diseased vessels.

in injury to the ribs, some of the free fluid globules of fat so derived may pass through the lung-capillaries (which otherwise usually act as filters of embolic matter) and then travel by way of the pulmonary veins and left side of the heart and so reach the brain by the systemic arteries. Small pyramidal or cone-shaped areas of infarction in the cerebral cortex, with their base at the surface and the apex perhaps reaching the subjacent white matter, have been traced to such fat-embolism as their cause.

Micro-organisms derived from the breaking-down of an infected thrombus in a vein may similarly be carried through the lung-capillaries and finally become lodged in the brain, leading to the production of **thrombosis** and later perhaps **pyæmic abscesses.** Yet another possible mechanism of the indirect spread of a systemic venous lesion to the brain by way of the lungs is by the production first of a pulmonary infarct by the blocking of a branch of the pulmonary artery, and then the subsequent spread to and involvement of the corresponding tributaries of the pulmonary vein, with embolism of the resulting clot through the left side of the heart. Partial, and even temporarily complete, obstruction without thrombosis, caused by irregular spasmodic contraction of the muscular coat of the vessel, is said to occur in arteries the lumina of which are already narrowed by degenerative and proliferative changes in their walls.

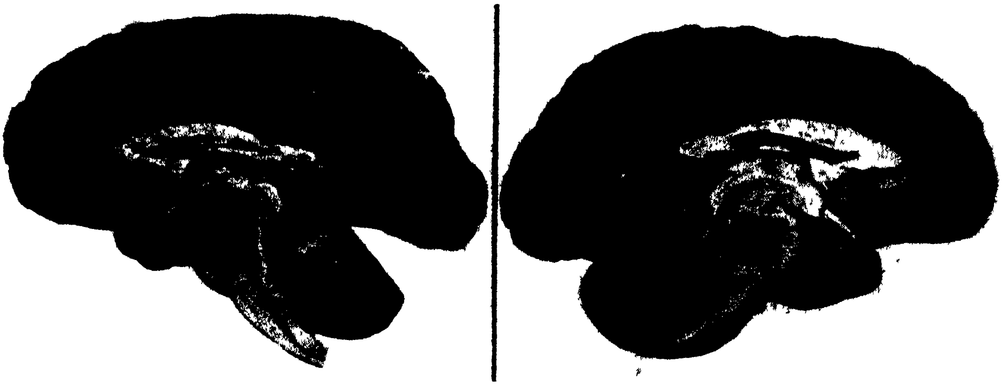


FIG. 620. *Cerebral thrombosis.* The brain of a man, aged fifty-three, previously a soldier, with chronic vegetative endocarditis, who had suffered from a series of attacks of cerebral embolism and thrombosis, the oldest being the *bilateral calcarine thrombosis* here illustrated, causing blindness of both retinæ (but with " sparing " of macular vision) of some twenty years' duration. On the mesial aspect of both occipital lobes the dark triangular hollows represent the sunken and destroyed cortical areas supplied by the blocked calcarine artery on each side (compare also Figs. 621 and 622). (Worster-Drought and Carnegie Dickson's case.—W.E.H.)

Thrombosis from causes other than embolism is less frequent and is usually secondary to degenerative change in the arteries, though in exceptional instances it may be due to enfeeblement of the circulation or to some abnormality of the blood.

Regions most liable to be affected by arterial obstruction: (*a*) **Embolism** occurs with greatest frequency in the **left** middle cerebral artery and its branches, on account of the position and direction of the origin of the **left** common carotid from the summit of the aortic arch just before the latter turns downwards to form the thoracic aorta; and also because of the direct continuity of the middle cerebral with the corresponding internal carotid—the

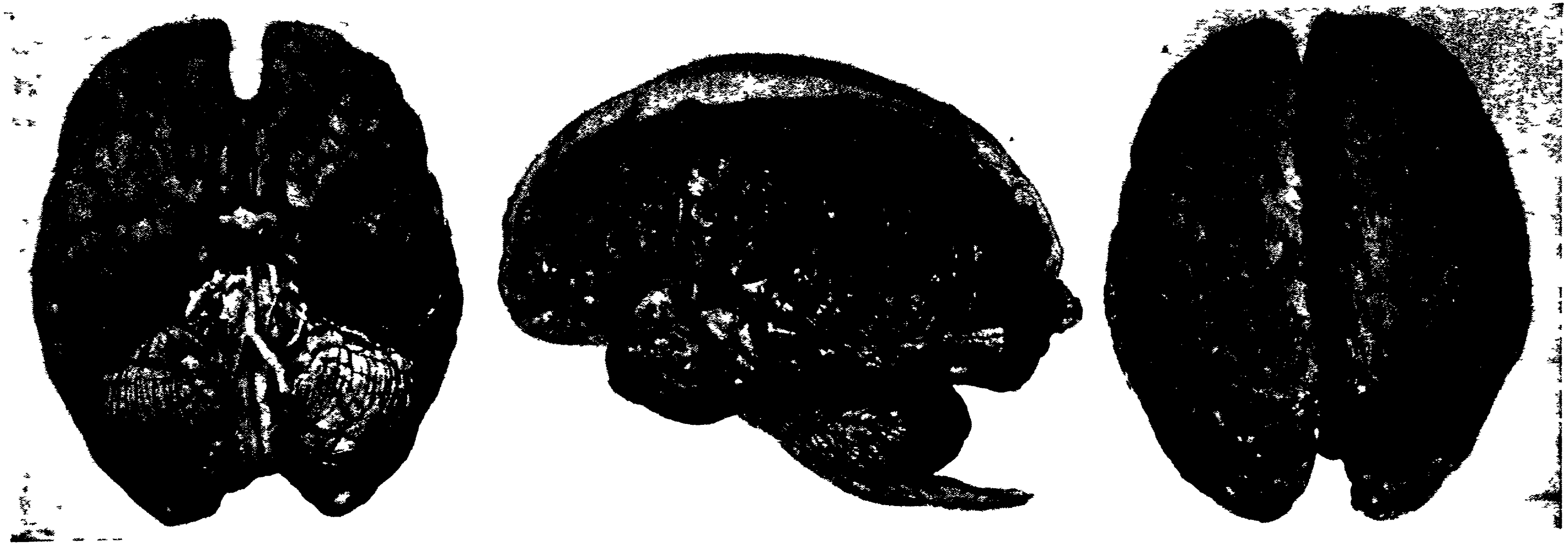


FIG. 621. *Bilateral calcarine thrombosis*. the same brain as that illustrated in Fig. 620. The basal aspect shows recent thrombosis of the left internal carotid artery, leading to intense meningeal congestion and hæmorrhage over especially the left temporal lobe and most of the left lateral aspect of the brain. An older thrombosis of a branch of the right posterior inferior cerebellar artery has produced the small deep cortical depression in the area of its distribution.

artery which, as just explained, by its anatomical course provides the most direct line of passage for an embolus (*cf.* p. 1053).[1] Next in order of liability come the right middle cerebral : the posterior cerebrals (the two sides being equally liable) : the vertebrals—the left more commonly than the right : the anterior cerebrals : the cerebellar, especially the posterior inferior cerebellar arteries : and the basilar, the last three, however, being comparatively rarely

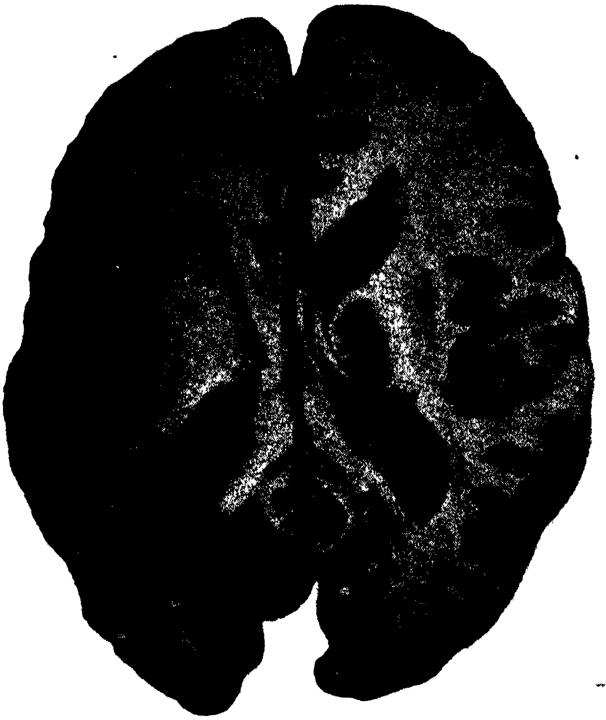


FIG. 622. *Bilateral calcarine thrombosis :* horizontal section, at level of corpus callosum (itself divided by a mesial longitudinal cut) of the same brain as that illustrated in Figs. 620 and 621, showing the results of the old thrombosis—destruction of the area striata on the medial aspects of both occipital lobes, with shrivelling of the brain-substance (the changes on the right side were more complete at a lower level than that shown), producing a retraction-hydrocephalus of especially the posterior horns. In the region of the left insula and the posterior portion of the left frontal cortex, a certain amount of necrotic softening and surface hæmorrhage have resulted from the blocking of the left internal carotid and middle cerebral arteries by recent thrombosis (*cf.* Fig. 621). (Worster-Drought and Carnegie Dickson's case —W.E.H.)

the seat of embolism. In an individual artery, the site of lodgment depends partly upon the size of the embolus and partly upon that of the vessel in which it lodges. In the blocked vessel, thrombosis takes place distally and sometimes to a certain extent proximally to the site of the embolic block.

(*b*) **Thrombosis** as a result of atheroma is found especially in branches of the posterior cerebral and the basilar arteries, or in some of the smaller cortical branches. When secondary to proliferative endarteritis, the thrombosis occurs particularly in the internal carotid and middle cerebral, and also in the basilar, the posterior cerebral and the vertebral arteries.

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[1] The late Professor W. S. Greenfield taught that, although embolism on the left side was commoner, the relative difference in frequency of the lesion in the left and right middle cerebrals respectively was only as 6 to 5. The above statements in the text as to the relative frequencies of both embolism and thrombosis in the various cerebral vessels are founded largely upon his extensive combined clinical and pathological experience.

Pathological Anatomy. In addition to the occurrence of the symptoms common to other cerebral lesions, the focal results of the obstruction, however caused, depend upon the site and extent of the damage produced, as well as on the condition of the arteries affected and the amount of collateral supply available. Thus complete blocking of the main trunk of the **middle cerebral artery** of one side will, in a widespread lesion involving its branches, both cortical and central, produce a hemiplegia of the opposite side of the body together with accompanying sensory loss of cortical type. If the **left** middle cerebral artery is the vessel affected, there will also be motor aphasia from involvement of Broca's area at the posterior end of the inferior frontal gyrus and its neighbourhood, together with impairment of the sensory comprehension of both written and spoken speech, due to involvement respectively of the cortical visual-word-area in the angular gyrus and of the auditory-word-area in the middle of the superior temporal gyrus. If the obstructing embolic mass be broken up into fragments, these will be distributed and cause multiple localised areas of damage ; and if one or more of the smaller branches of the artery are blocked, the results will vary accordingly. For example, embolism or thrombosis of the left inferior external frontal branch will produce these impairments of the functions of Broca's speech-centre in the left lower frontal convolution. Thrombosis of the **calcarine branch of the posterior cerebral artery** (Figs. 620–622) leads to blindness, varying in its degree and distribution according to the extent and position of the damage to the visual cortex on the medial aspect of the occipital lobe, central or macular vision not infrequently escaping, even when there is otherwise complete loss of peripheral or panoramic vision. Thrombosis of the **basilar** artery will cause softening in the pons and may give

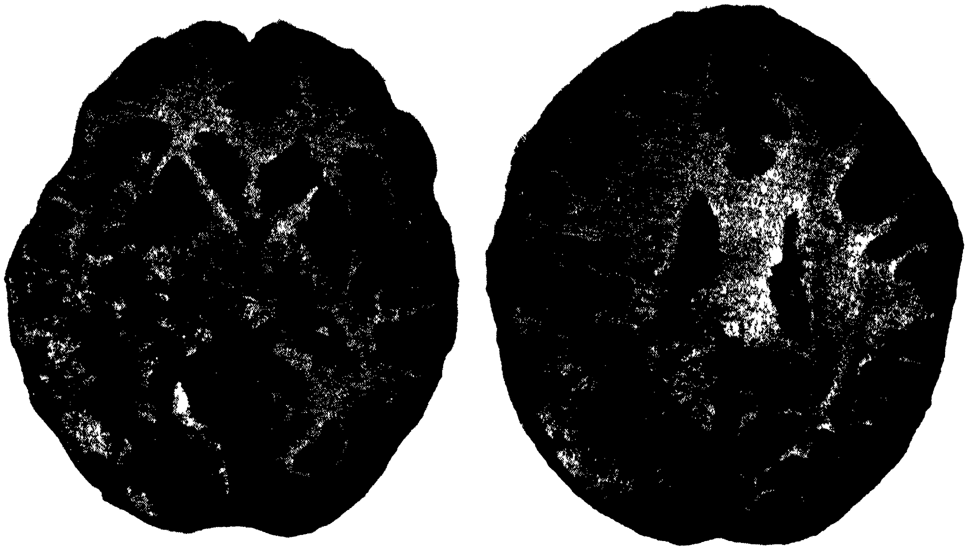

FIG. 623. *Thrombosis of basilar and left posterior cerebral arteries* following upon an intravascular injection of thorotrast (see text) in a woman, aged fifty-eight. The lesion is practically a large infarct and shows combination of softening (encephalomalacia) and patchy hæmorrhage.

rise to quadriplegia. The nutrient arteries supplying the brain-substance do not anastomose freely with one another, and their occlusion has very serious results, this being also the case with the central artery of the retina, embolism of which causes sudden blindness and destruction of the retina (p. 178 and first footnote). On the other hand, obstruction of some vessels in the circulus arteriosus (circle of Willis), where the anastomosis is free, may lead merely to a temporary derangement of the circulation.

Phenomena observed as a Result of Arterial Obstruction. Within a few hours after the obstruction, in cases which do not immediately succumb to its effects, there is hyperæmia of the pia-mater—if the lesion be cortical—and in those parts of the brain bordering on the region from which the arterial supply has been cut off. This hyperæmia, especially of the cerebral substance, soon passes off, and, unless complicated by the occurrence of hæmorrhage, the parts supplied by the obstructed artery become pale and soft. Gradually this softening—**encephalomalacia**—becomes more pronounced and the affected part is converted into a mass of creamy pulp which can be easily washed away under a gentle stream of water from the tap. If in the interior of the brain, partial absorption may similarly take place, and a smooth-walled pseudocystic cavity containing somewhat turbid fluid generally remains (p. 178). Usually this cavity has no distinct cyst-wall, and there is as a rule no deposit of pigment such as is seen after hæmorrhage. Unless secondary extension of the necrotic softening supervenes (*e.g.* from a further spread of the thrombosis in the vessels, or from hæmorrhage and consequent bruising and œdema of the brain-tissue), the softened area is smaller than the area supplied by the obstructed artery. If the lesion is small, it may eventually be replaced by a patch of glial sclerosis, producing, if near the surface, a superficial depression (Figs. 620 and 621).

On microscopical examination, the nerve-fibres are found to be disintegrated, the myelin undergoes fragmentation and escapes from the nerve-sheaths. The nerve-cells are slightly more resistant than the fibres, but they also degenerate and eventually disappear. The microglial cells (as well as endothelial cells surrounding and lining the vessels) become detached and, re-acquiring motility, act as scavengers, taking up the degeneration-products of the myelin and other tissue-elements, thus becoming loaded with fatty globules and debris and constituting the phagocytic cells characteristic of such lesions and known variously as "compound granular corpuscles," "gitter-cells" or "foam-cells" (p. 956). Hæmorrhage in varying amount may be present in some cases, but the hæmoglobin gradually dissolves out from the red corpuscles and is diffused throughout the tissues. Thus the red colour of these softenings accompanied by hæmorrhage (red softening) gradually changes to yellow (yellow softening) and then to white (white softening). Wallerian degeneration, secondary to the destruction of nerve-cells or the interruption of nerve-fibres, will follow such lesions according to their situation and extent.

Thrombosis of the Cerebral Veins and Intracranial Venous Sinuses has already been described in connection with Diseases of the Membranes of the Brain (p. 973). So-called "primary" thrombosis of superficial and other cerebral veins may occur from any of the causes enumerated on pp. 166 and 500–1, but in the majority of cases is seen in women after childbirth. When "secondary" to spread from neighbouring structures, middle-ear infection is one of its commonest causes (pp. 973–4 and 979).

INTRACRANIAL HÆMORRHAGE

Under this term are included two series of lesions—hæmorrhage into or upon the surface of the membranes of the brain—**meningeal hæmorrhage**—and hæmorrhage into the substance of the brain or **cerebral hæmorrhage** proper.

Epidural or **extradural** and **intradural** hæmorrhages are described on p. 974 : **subdural** hæmorrhages on pp. 974–7 : and **subarachnoid** hæmorrhage on p. 977. Hæmorrhages due to the **leakage** or **rupture of aneurysms** of the larger intracranial arteries and their branches are considered separately on p. 1042 *et seq.*

CEREBRAL HÆMORRHAGE (“ **cerebral apoplexy** ”) is due most frequently to rupture of blood-vessels within the substance of the brain. These hæmorrhages may vary in size from minute pin-point or petechial lesions, often multiple and widely scattered, produced by the destruction and giving way of the endothelium of capillaries, up to massive and extensive effusions due to rupture, or sometimes a series of ruptures, of diseased arteries.

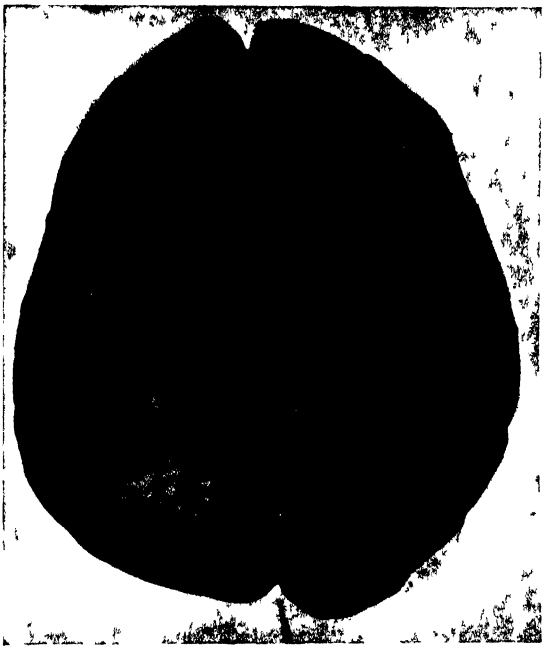

FIG. 624. Large cerebral hæmorrhage into region of the internal capsule and basal ganglia.

Many of the more immediate **causes** leading to the production of intracerebral hæmorrhage are similar to or identical with those already enumerated in some detail for meningeal hæmorrhage (p. 974), for example, trauma, acute inflammatory and toxic diseases, phosphorus-poisoning, and also any severe anæmia and the leukæmias. The most important contributory causes are pre-existing disease of the arteries themselves such as atheroma : high blood-pressure or hyperpiesis, with or without renal disease : and some rarer conditions such as congenital stenosis (coarctation) of the aorta : and especially when there is any sudden superadded increase of pressure from muscular exertion, violent coughing, straining at stool or the like. For hypoprothrombinæmia as a cause of intracranial hæmorrhage in new-born infants, *see* pp. 161 and 588.

Hæmorrhages of varying size and severity **into or from cerebral tumours** are of common occurrence, especially in the more malignant types such as glioblastoma multiforme (p. 1103) or in cerebral metastases from malignant tumours elsewhere, and such bleeding may sometimes be precipitated by lumbar puncture (Figs. 625 and 626). **Another by no means negligible risk of haemorrhage** occurs during the carrying out of **exploratory brain-puncture** for ventriculography and other diagnostic procedures. When the lateral ventricles are, as is often the case, considerably displaced from their normal position and perhaps *not* dilated (as in Fig. 629), the needle may easily penetrate important adjacent structures such as **the internal capsule** and cause hæmorrhage and a certain amount of necrosis, which may result in hemiplegia and hemianæsthesia of the opposite side of the body, from which complete recovery may not always be possible (Figs. 629 and 630).

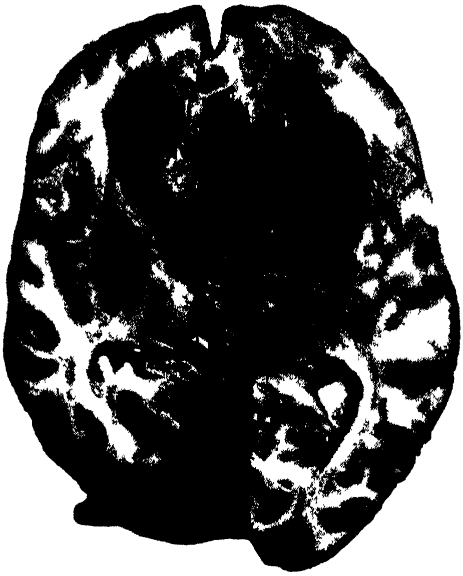

FIG. 625. *Hæmorrhage following lumbar puncture in a man of fifty four years with cerebral tumour.* The extensive bleeding into and from a large glioblastoma multiforme in the anterior half of the right hemisphere supervened immediately after the lowering of the intracranial pressure by lumbar puncture. The tumour itself was so ploughed up and obscured by the hæmorrhage that its presence had to be confirmed microscopically.

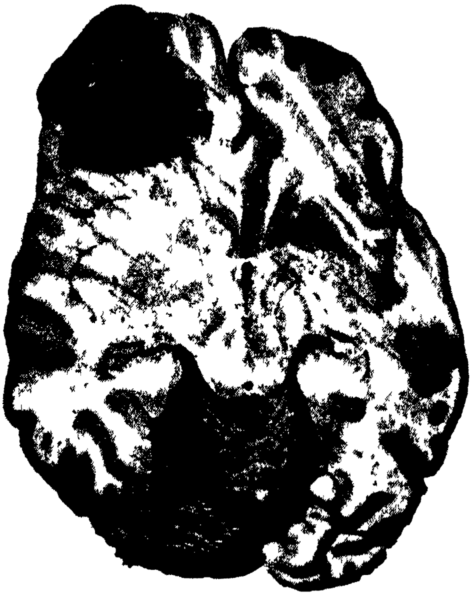

FIG. 626. *Hæmorrhage following lumbar puncture in a case of secondary malignant tumour* of unknown origin (the examination was limited to the head) in a woman of thirty six years. The bleeding occurred at the deep aspect of the tumour which had thus been dislocated forwards out of its bed in the left frontal lobe.

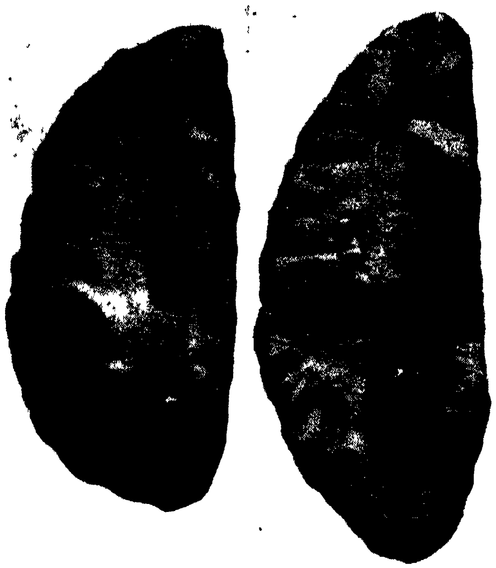

FIG. 627. *Exploratory needle-track hæmorrhages* in occipital lobe and lateral ventricle of a female patient, aged fifty-four years, operated on for chronic hydrocephalus caused by old adhesions in the ependymo-pial roof of fourth ventricle.

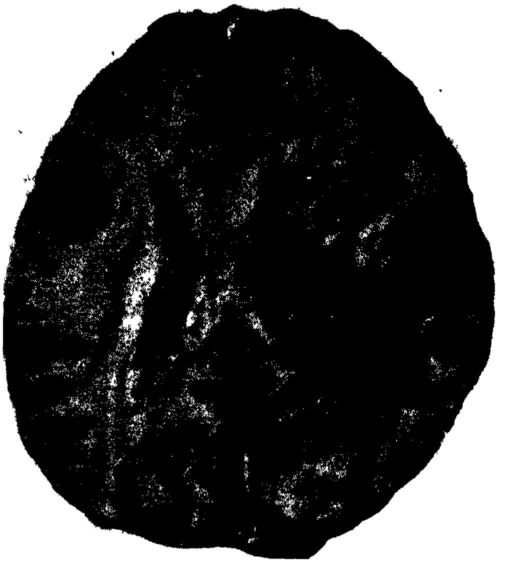

FIG. 628. *Extensive hæmorrhage and cerebral softening following an injection of " thorotrast " into the right ventricle* for ventriculography in a man, aged fifty-two years, with advanced arteriosclerosis. (*See also* Fig. 619 (B), p. 1029, showing thrombosis of the left vertebral and other cerebral arteries in the same case.)

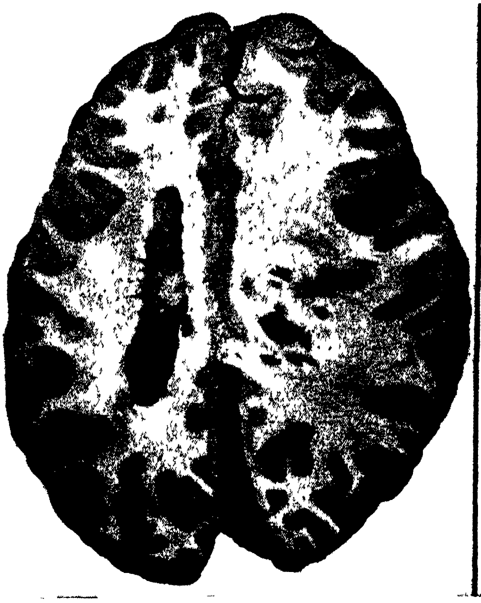

FIG. 629. *Multiple exploratory needle-track hæmorrhages* in region of right internal capsule in a female, aged thirty-nine years, operated on for a meningioma at a level below the mottled area of cortex seen in posterior part of frontal cortex. The cavity of the right lateral ventricle was compressed by the tumour and pushed to the left. Fluid blood was present in the left lateral ventricle from the small puncture-wound on its inner wall.

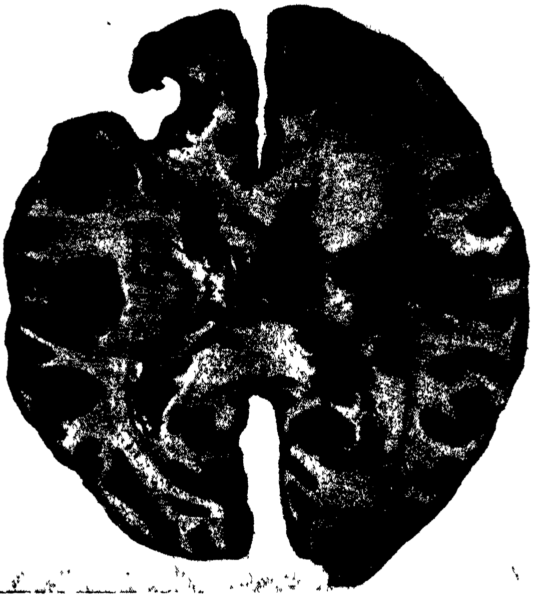

Fig. 630. *Multiple exploratory needle-track hæmorrhages* in region of internal capsule in a female patient, aged fifty-two years, operated on for meningioma. Had these patients survived, they would have suffered from various degrees of paralysis and anæsthesia of the opposite side of the body.

Apart from the various definite causes enumerated above, the presence of ***minute aneurysms***, miliary,[1] submiliary or perhaps only microscopic in size, on the smaller arteries within the cerebral substance, especially on branches of the middle cerebral artery in the region of the basal ganglia, has, since the time of Charcot (1868), been looked upon by many writers as an essential preliminary to the occurrence of typical " spontaneous " cerebral hæmorrhage ; but the existence of these small aneurysms has been doubted or denied by a number of subsequent investigators, including Eppinger (1887), Pick (1910) and Turnbull (1914–15). Our own view is that, though by no means a constant or even predominant cause, they do sometimes occur, as for example in two out of ten cases investigated by Green,[2] to which further reference is made on pp. 1042–3.

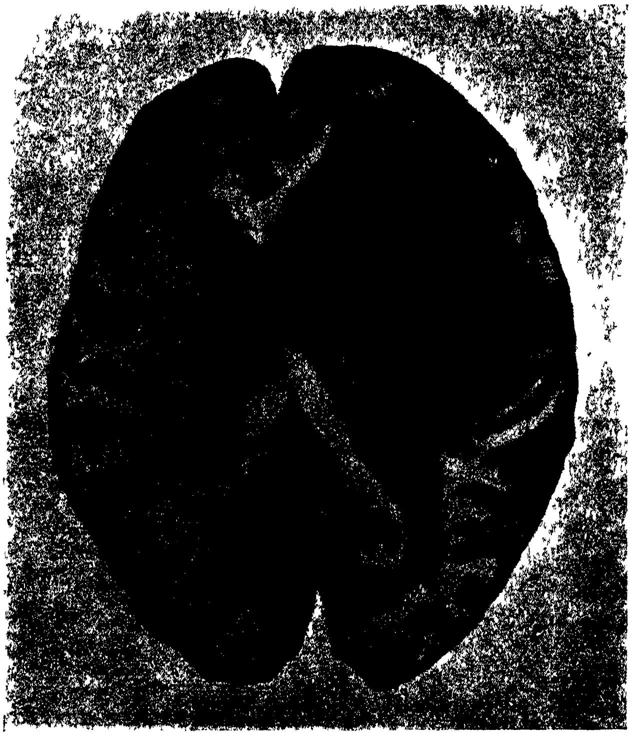

FIG. 631. *Large cerebral hæmorrhage* in an elderly male in the region of the basal ganglia, which has burst into the ventricles.

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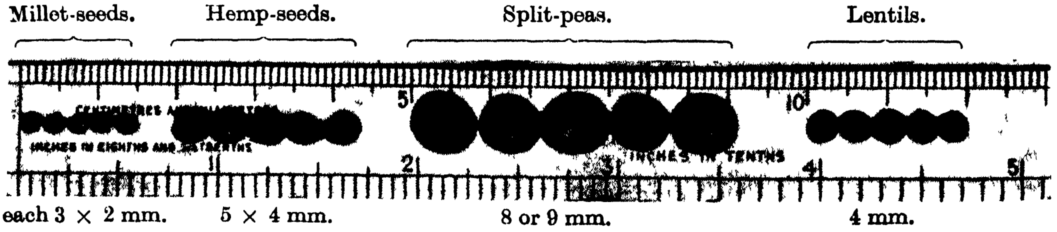
[1] The term " miliary " is so often and perhaps rather vaguely used in pathology as a descriptive term for various small lesions that the annexed scale-diagram of millet-seeds, etc., bought at the nearest grocer's, may interest and perhaps even amuse our readers.



[2] " Miliary Aneurysms in the Brain," by F. H. K. Green, St. Bartholomew's Hospital, London, *Journal of Pathology and Bacteriology*, 1930, **33**, 71.

Sites of Cerebral Hæmorrhage. According to the teaching of the late Professor W. S. Greenfield, the commoner situations in which hæmorrhage takes place are, in order of importance :—

1. In the vicinity of the **basal ganglia** (75 per cent.), at the upper part of the external capsule (Fig. 632, p. 1040); also towards the upper and outer part of the lentiform nucleus ; or in the adjoining part of the internal capsule —from any of which sites it may spread and involve the centrum ovale, or destroy the basal ganglia and burst into the lateral ventricles (Fig. 631).
2. In the **pons** (10–12 per cent.), where also pigmented areas, representing the situations of old hæmorrhage, are often seen in cases of renal disease or in general arteriosclerosis.
3. In the **meninges** (12 per cent.—already considered on p. 974).
4. In the **cerebellum** (1 per cent. or less).
5. In more than one site, *e.g.* in basal ganglia *and* pons.

Unless due to hæmorrhage from tumour, **ventricular hæmorrhage** is almost always secondary to bleeding into the substance of the brain, originating most frequently from the smaller branches of the anterior and the posterior cerebral arteries—the former at the tip of the caudate nucleus, the latter at the posterior end of the thalamus—or from the middle cerebral artery.

Blood thus extravasated into one of the lateral ventricles is likely, in varying admixture with cerebrospinal fluid, to find its way through the third, into the opposite lateral, ventricle and down along the rest of the ventricular system to the base, whence it may be diffused in the subarachnoid space over the surface of the brain and down into the spinal theca, in which its presence may be detected on lumbar puncture. If present in sufficient amount and concentration, the blood coagulates and the ventricular system may at death be found to contain clotted blood (Fig. 631).

The Characters and Results of Hæmorrhage. The amount of the hæmorrhage and of the resulting blood-clot depend to a certain extent on the size of the ruptured vessel and on the nature of its support and surroundings. If rupture takes place into the white matter of the centrum ovale, the blood tends to spread widely, pushing its way along the lines of the nerve-fibres and perivascular spaces. The affected hemisphere often appears bulkier than that of the other side and its convolutions more distinctly flattened. In the case of rupture into the internal capsule, the spread may be less extensive. The brain-tissue is lacerated and contused, and, as evidence of such contusion, numerous punctate hæmorrhages are seen in the softened and perhaps slightly yellowish and discoloured brain-tissue around the larger hæmorrhage. Some surrounding œdema may follow, causing an increase in the extent of the damaged area. A **series** of hæmorrhages at different times may occur either from the same vessel or from vessels around the primary hæmorrhagic area. These sometimes coalesce and produce extensive softening and destruction of the brain-tissue—**encephalomalacia**—and the changes described on p. 1034 ensue (*see also* p. 249), phagocytosis of the broken-down tissue by foam-cells being usually a prominent feature.

If the hæmorrhage does not prove immediately fatal, absorption, partial or complete according to the size of the original lesion, takes place. The hæmoglobin is freed from the red corpuscles, part of it being transformed into hæmosiderin, and part deposited as hæmatoidin-crystals. Granulation-tissue is formed, but collagen-fibres are usually scanty. The surrounding neuroglial tissue proliferates to a limited extent and there is thus produced a smooth-walled pseudocyst filled with brownish or perhaps ultimately colourless fluid, the so-called "**apoplectic cyst,**" often with a varying amount of brownish or yellowish blood-pigment in the tissue around it, together with varying numbers of mixed astrocytes and fibroblasts and their fibres, any collagenous tissue being derived from that of pre-existing vessels or around capillaries derived from these. Several such cysts of varying size and age may be found in individual cases, indicating the occurrence at different times of a series of previous hæmorrhages. Some contraction of the brain-tissue in the neighbourhood usually follows. Acute softening may occur round the old hæmorrhage.

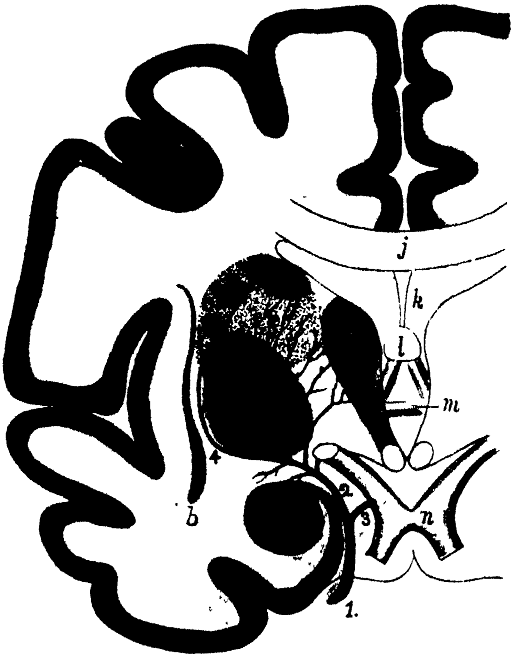


FIG. 632. Diagrammatic view of the basal ganglia and their blood-supply, seen in coronal section.

a. Insula or island of Reil and its covering opercula. *b*. Claustrum. *c*. External capsule. *d*. Lentiform nucleus (its divisions not shown). *e*. Internal capsule. *f*. Caudate nucleus. *g*. Thalamus. *h*. Amygdaloid nucleus. *j*. Corpus callosum. *k*. Lateral ventricles with septum pellucidum between them. *l*. Fornix and its anterior columns. *m*. Anterior commissure crossing third ventricle, *n*. Optic nerves, chiasma and tracts.

1. Internal carotid artery and its continuation as : 2, the middle cerebral artery, giving off : 3, anterior cerebral artery, and 4, the medial and lateral striate arteries, of which the outermost and largest is the direct continuation of the middle cerebral, and has been called the "artery of cerebral hæmorrhage" (*see* description in text). The stippled part of the diagram represents the area in which hæmorrhage most frequently occurs—the three darker spots indicating the common sites of origin of such hæmorrhage.

Hæmorrhage from the Middle Cerebral Artery. Of the branches of the middle cerebral artery which pass through the anterior perforated space, some are given off directly into the substance of the lentiform nucleus. One, the

lenticulo-striate—sometimes merely the largest of a group of such branches (Fig. 632)—passes between the lentiform nucleus and the claustrum, and enters the caudate nucleus. Rupture of this vessel (previously known as the lenticulo-striate artery) is of such frequent occurrence that it was termed by Charcot "the artery of cerebral hæmorrhage." The starting-point of the hæmorrhage from this vessel is frequently in the external capsule or in the outer part of the lentiform nucleus, the blood ploughing its way into the nucleus through the important conducting nerve-fibres of the internal capsule and reaching as far even as the lateral ventricle. If the hæmorrhage in these situations is near the anterior end of the nucleus, it may spread into the centrum ovale. Hæmorrhage in the region of the claustrum is not uncommon, and forms a barrier, often linear in outline, separating the lentiform nucleus from the insula or island of Reil. Hæmorrhage into the internal capsule is thus sometimes an extension of these more external or laterally placed hæmorrhages, though rupture of the lenticulo-striate branch may in other instances involve primarily the motor part of the capsule, *i.e.*, the anterior two-thirds of the posterior limb and the genu; whilst hæmorrhage from the lenticulo-optic branch may spread to and destroy the sensory fibres in the posterior third of the posterior limb of the capsule.

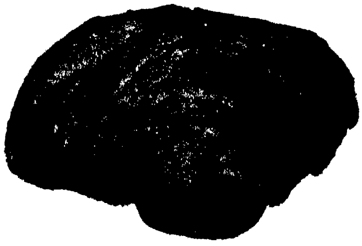


FIG. 633. *Hæmorrhage into the pons.*

Hæmorrhage from the Anterior Cerebral Artery. The branches of this artery which give rise to cerebral hæmorrhage are more especially those which supply the anterior part of the caudate nucleus, particularly that part of it projecting into the lateral ventricle. Thus this artery is one of the commonest sources of **ventricular** hæmorrhage, which, however, can also result from rupture of the branch of the **posterior cerebral artery** which supplies the thalamus.

Hæmorrhage into the Pons comes next in frequency to that into the basal ganglia. Such pontine hæmorrhages may occur independently or may be part of a more extensive lesion which has tracked downwards through the mid-brain from above; but they are found sometimes as a complication of a larger hæmorrhage at a higher level, though not necessarily in actual continuity with it. They may then be due to the action of the increased intracranial tension upon perhaps already diseased pontine vessels, and to a displacement of the parts, analogous to the hæmorrhages now recognised as liable to be produced in accident-cases from the sudden and violent jarring of the brain-stem and neighbouring structures against the firm edge of the immobile incisura tentorii (p. 1023). This may cause, not only concussion and contusion around the aqueduct, but even fatal hæmorrhage into and from the floor of the fourth ventricle. Such pontine hæmorrhages are of varying size, sometimes small and multiple and not necessarily taking place simultaneously, but in sequence: sometimes larger and causing destruction of perhaps a considerable portion of the substance of the pons.

Hæmorrhage into the Cerebellum, apart from its occurrence as a complication of tumours, is uncommon.

INTRACRANIAL ANEURYSMS (p. 495). Aneurysms upon the cerebral vessels are by no means rare and have now often been diagnosed comparatively early in their course by the procedure of X-ray angiography following immediately upon the injection ot a radio-opaque substance into the affected vessels,[1] and also later from the development of calcification in their walls; whereas, until comparatively recently, attention was not infrequently first called to the presence of such an aneurysm only by its actual rupture. Edwin Bramwell (1934) makes the convenient clinical classification of intracranial aneurysms into the two groups: (1) the **apoplectic,** in which leakage or rupture occurs: and (2) the **paralytic,** producing symptoms by their physical presence and pressure upon nerves and other important structures.

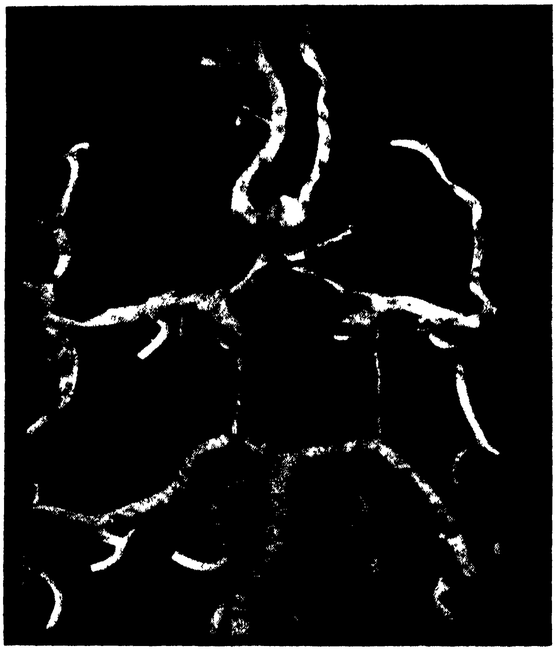


FIG. 634. *Two small aneurysms on arteries of the circulus arteriosus* at the base of the brain in a woman aged fifty years. The vessels showed opaque patches of atheromatous thickening, the basilar being dilated and tortuous. On the right middle cerebral, about an inch from its origin, is a small spheroidal aneurysm about the size of a large pea; and on the anterior communicating artery a second slightly larger aneurysm which had ruptured and given rise to an extensive basal hæmorrhage. (Dr. W. M. Ord's specimen.[2])

In connection with the causation of cerebral hæmorrhage, reference has already been made on p. 1038 to the problem of the existence or not of multiple "miliary" or "submiliary" aneurysms upon the deep nutrient arteries in the substance of the brain.

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[1] This procedure is not always unattended by danger, for example when substances such as "thorotrast" have been used, and especially where the lesion has proved to be other than the aneurysm suspected, for example certain tumours in which serious reactive or necrotic changes may be set up—as may happen also in the case of an aneurysm in which thrombosis has already occurred (*cf.* p. 1059).

[2] "Aneurysm of the anterior communicating artery of the circle of Willis," by W. M. Ord, *Transactions of the Pathological Society of London,* 1881, **32,** 65.

These undoubtedly do sometimes occur, for example, upon branches of the middle cerebral artery to the basal ganglia ; but they do not appear to be demonstrable in more than a comparatively small proportion of cases of hæmorrhage from these vessels. Search may be made for them either by cautiously washing away the softened brain-substance and blood-clot from around the suspected vessels, or by fixing the brain and making serial sections, though this is sometimes difficult or even impossible where the hæmorrhage has caused extensive destruction. Three such small or "submiliary" aneurysms found by Green [1] in cases which had died of lenticulo-striate hæmorrhage were about 0.5 mm. in diameter, the parent vessels showing gross atheromatous degeneration.

Larger aneurysms, often, but not invariably, single, may be developed upon any of the cerebral arteries, and are found especially on the vessels of the circulus arteriosus or circle of Willis or any of its branches, as well as upon the internal carotid, vertebral, or basilar arteries. Of a series of ten cases of intracranial aneurysm, published by Drennan [2] (1921)—excluding two which were due to infective embolism—the remaining eight were all upon the **anterior communicating artery,** five of them at its angle of origin from the left anterior cerebral artery, where, Professor Drennan points out, the vessel-wall may be weakened by the giving off of one, or perhaps two, small twigs, as indicated in his diagram which we annex here. Of these eight cases, with an average age of forty-six years, five were in females, three in males. Attention was drawn many years ago by the late Professor W. S. Greenfield to the occurrence of aneurysm of the anterior communicating artery.[3] Such aneurysms vary in size, most commonly from a few millimetres up to 2 or 3 cm. in diameter, *i.e.*, from, say, the size of a small pea up to a cherry or a walnut, though they occasionally attain a much larger size. They are most frequently saccular in type. As they occur, not only in middle-aged and elderly, but also in younger, persons—adolescents and young adults ; are only occasionally multiple ; and, especially in the younger patients, are often situated upon otherwise healthy vessels, they are thought to be due to **congenital** weakness of the vessel-walls. They are found especially at the bifurcations of the cerebral

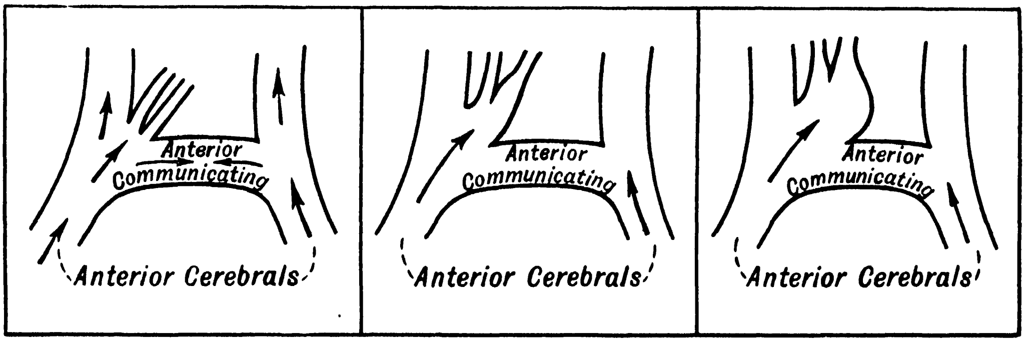

FIG. 635. *Diagram* illustrating the mechanism of production of *Aneurysms of the anterior communicating artery,* as suggested by A. M. Drennan (*see* text).

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[1] *See* second footnote on p. 1038.

[2] "Aneurysms of the Larger Cerebral Vessels," by A. M. Drennan (Otago and Edinburgh), Wellington, New Zealand, 1921.

[3] "Aneurysm of the anterior communicating artery ; rupture ; subarachnoid hæmorrhage," *Transactions of the Pathological Society of London,* 1876, **27**, 2.

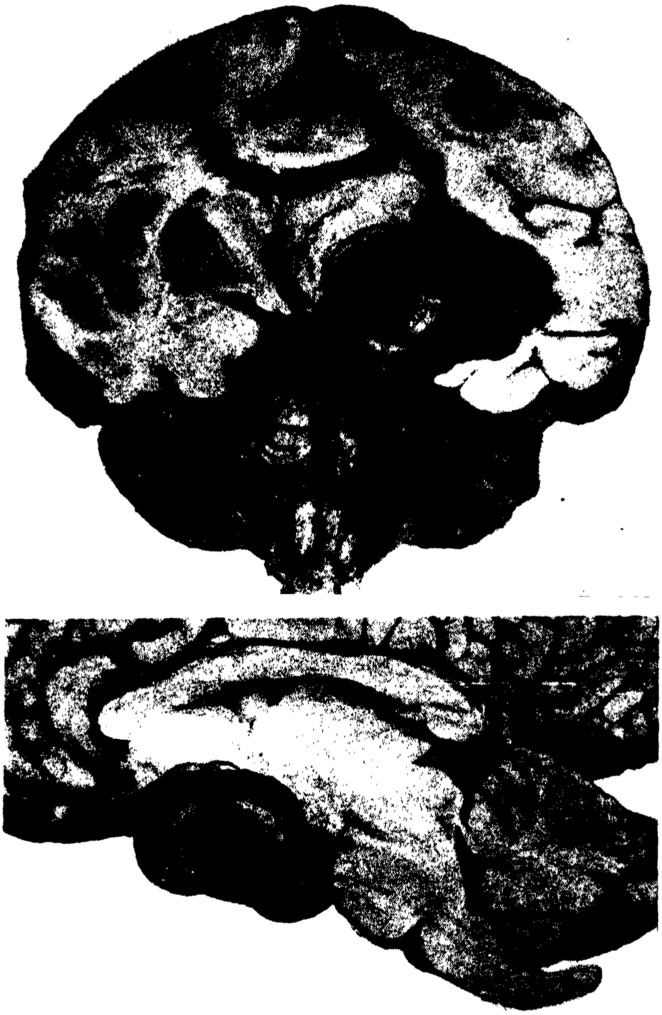

FIG. 636. *Intracranial Aneurysms:* (Upper). Coronal section of brain showing an aneurysm (measuring from 31 to 33 mm. in its various diameters) *involving vessels of left side of circulus arteriosus* (*circle of Willis*) in a female, aged thirty-six years, with recurring subarachnoid hæmorrhage and terminal rupture. (Case of the late Dr. Macnamara, W.E.H.) Approximately two-thirds natural size.

(Lower). Mesial sagittal section of brain of a man, aged forty-four years, showing an aneurysm (measuring 35 × 25 × 30 mm.) *on the anterior communicating artery.* It contains partially decolourised laminated clot. The symptoms simulated those of pituitary tumour, but that gland is seen immediately below and behind the aneurysm. There was a ten years' history of gradually increasing bitemporal hemianopia and optic atrophy. (Dr. Worster-Drought's case, W.E.H.) Approximately half natural size.

arteries, where a local deficiency of muscle-fibres has been detected similar to that found in the media at the points of junction of any two component arteries of the circle of Willis. In some of the published series of cases,[1] intracranial aneurysms of this " congenital " type affecting the circle of Willis and its branches are commoner in the female than in the male—in the latter, on the other hand, as explained on p. 493, ordinary acquired aneurysms, found elsewhere and often syphilitic in origin, are of more frequent occurrence than in women.

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[1] Geoffrey Jefferson (1937), " Compression of the Chiasma, Optic Nerves and Optic Tracts by Intracranial Aneurysms," *Brain*, 1937, **60**, 444. This author contributes 12 new cases of basal aneurysm affecting the visual pathways and analyses 66 previously recorded cases. Of this total of 78 cases, 44 were in women. He also describes 16 cases of congenital saccular aneurysm of the internal carotid in the cavernous sinus (*Medical Annual*, 1940, p. 47, and *Brit. Jour. Surg.*, 1938, **26**, 267).

Although such local and inherent structural weakness in the media of the cerebral arteries is thus itself apparently congenital in nature, and the aneurysms developing at these sites may also therefore be termed "congenital," the actual process of dilatation need not necessarily commence at an early age, but may supervene at any period of life.

An analogous explanation of " inherent weakness " is also not improbable in the case of the so-called **" subclinoid " aneurysms of the internal carotid artery.** On the cervical portion of this vessel saccular aneurysms are rare, but they are not uncommon on the **intracranial** continuation of its course. Jefferson (1938) suggests that its S-shaped curve, although serving mechanically to protect the brain from the too violent transmission of the impact of the bloodstream at each heart-beat, or from sudden alterations of blood-pressure, may in some instances be an inherent source of weakness to the vessel-wall itself. In the same sense as that already explained above, this weakness may perhaps in certain instances be regarded as being of a " congenital " nature ; and such aneurysms occur in women from the age of thirty years or more, but are correspondingly uncommon in men. According to their position within the cavernous sinus, these subclinoid saccular aneurysms of the internal carotid will produce sensory and other symptoms by compressing the ophthalmic division of the fifth cranial nerve, and paresis or paralysis of the muscles which move the eyeball by pressure on the third, fourth and sixth nerves. It has been noted, however, that such aneurysms are less apt to involve the optic nerves themselves than are meningiomatous tumours of this region.

These " congenital " aneurysms occur independently of the presence of arteriosclerosis, high blood-pressure, renal disease and hypertrophy of the left ventricle ; but, if these factors supervene, they will aid in the formation and increase the size of the aneurysms, and may bring about their rupture, as may also some sudden or violent physical exertion. Such rupture may rapidly cause death, or the patient may survive for a varying period or even partially recover—in which case there is liability to recurrences of the subarachnoid bleeding, varying in severity, and sometimes merely a recurring leakage with evidence of bleeding into the subarachnoid space (pp. 977–8). In some instances, especially where there has been sudden and forcible rupture, the adjacent brain-tissue is extensively lacerated by the extravasated blood, as in the upper specimen shown in Fig. 636.

Pressure-symptoms, general and focal, will resemble those produced by any slow-growing intracranial tumour. Pressure upon the optic tracts, chiasma or optic nerves, or upon the third, fourth and sixth or other cranial nerves, or upon various portions of the brain itself, will produce symptoms by which the site of the aneurysms can be diagnosed ; whilst leakage or rupture will lead to the phenomena in the cerebrospinal fluid described on pp. 959 and 977–8.

Aneurysms other than those of the foregoing congenital type are less common. **Embolic aneurysms** are produced by impaction, most frequently in the middle cerebral arteries or their branches, of infective emboli containing micro-organisms of low virulence, *e.g.*, vegetations from heart-valves in subacute infective endocarditis. If organisms of greater virulence are present, the resulting lesion is more likely to be a pyæmic abscess. **Polyarteritis acuta nodosa,** a disease of obscure origin, is characterised by the presence of numerous small and usually thrombosed or thrombosing aneurysms upon many of the smaller arteries of the body including those of the brain (p. 478).

Arteriosclerosis and syphilis, although often associated with the presence and production of aneurysms elsewhere, are not now regarded as such common or important causes of intracranial aneurysm as they were formerly believed to be.

Traumatic aneurysms occasionally follow damage to certain of the intracranial arteries in fracture, *e.g.*, of the base of the skull. **An arterio-venous** aneurysm between the internal carotid artery and the cavernous sinus may be thus produced, with exophthalmos on the affected side.

SECTION VIII

INFLAMMATION OF THE BRAIN

ENCEPHALITIS, ACUTE, SUBACUTE AND CHRONIC

For the proper development and continuance in health of the nervous system, central and peripheral—in addition to many other factors, amongst which are included a suitably balanced diet—an adequate supply of **vitamins,**[1] particularly the inter-dependent vitamins A and B_1, and the presence of other associated factors such as **co-enzyme activity** and the co-operation of certain of the **ductless glands,** especially thyroid and supra-renal cortex (Chapter XXIV, p. 806 *et seq.*), are essential. **Vitamin A, biosterin," the anti-infective agent,"** is, as pointed out by Edward Mellanby (1935), necessary for the integrity of the nervous system, especially of the young ; and deficiency or absence of this vitamin results, not only in an unhealthy state of epithelial structures such as the mucous membranes, but also in various degenerative conditions in nerve-cells, and in " night-blindness " from inability to regenerate visual purple (p. 440). Deficiency in **vitamin B_1, aneurin** or **vitamin F**—as is implied by the descriptive term **" the anti-neuritic factor "** applied to it—leads to the production of various forms of **" polyneuritis,"** including that characteristic of **beri-beri** (pp. 444–5 and 1077). An analogous deficiency of **vitamin B_2, riboflavin (lactoflavin, ovoflavin,** etc.), also known as **vitamin G,** leads to the production of **pellagra**—aided probably by an associated deficiency of **vitamin B_6** (**" adermin "** or **vitamin H**) (pp. 444–5). The symptoms and lesions of pellagra include various skin-troubles, glossitis, and the demyelination of certain tracts in the spinal cord and peripheral nerve-fibres, with the production in some instances of **subacute combined degeneration** (p. 1157 *et seq.*) and varying degrees of paresis and paralysis, as well as serious mental symptoms, extreme emaciation and debility. Vitamin B_6 has been used, apparently with some success, for the treatment of pseudohypertrophic muscular dystrophy (p. 1243), as well as of beri-beri and pellagra, the macrocytic anæmia of pellagrins improving rapidly on its intravenous administration.

The varieties of the inflammatory process and the routes by which infective and other noxious agents reach the tissues and organs of the body are discussed in Chapter II (p. 15). By applying the general principles there laid down concerning the phenomena of inflammation, degeneration, and repair, to his knowledge of the gross and minute structural peculiarities of the nervous system, the reader will be able to infer for himself many of the characters of the lesions, acute and chronic, produced by these processes.

In inflammation, the meninges, with their endothelial (mesothelial) lining-cells, blood-vessels, and connective tissue, and the ventricular ependyma with its supporting glia, show all the usual vascular and cellular phenomena of the inflammatory process, but the exudate produced by a meningitis or an endoventriculitis is modified by its admixture with the cerebrospinal fluid present in the subarachnoid spaces and ventricular system. In the substance of the neuraxis (the brain and spinal cord), the delicate nerve-cells and their processes are liable to **degenerative** changes from which recovery may be incomplete or which may be followed by their disintegration and disappearance. Damage to the **nerve-cell** leads to **secondary degeneration** of the axis-cylinder process or **axon** and its various sheaths, including fragmentation and disintegration of the myelin itself. These degenerations, of all degrees of severity up to complete Wallerian degeneration, are described in Textbooks of Physiology,[2] and can be studied in the nerve-tracts of the white matter of the neuraxis and in the cranial, spinal and other nerves.

The supporting **neuroglia** takes part in both acute and chronic inflammatory processes, but it is the **chronic proliferative reactions** and the **sclerosis** resulting from these that constitute the especially characteristic *rôle* played by the glial tissues.

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[1] The problem of the unscientific devitaminising of wheaten flour by over-milling, and the consequent devitalising of our populations, is now being investigated both in Britain and America ; and, owing to the successful and not too costly synthetic manufacture of crystalline thiamin, riboflavin and nicotinic acid, it is now considered possible to "recharge" with them the white flour for which there is still such an unfortunate popular demand. Vitamin-C tablets are also now being added to the milk of school-children as a war-time measure.

[2] Schafer's " Essentials of Histology," 14th edition, edited by H. M. Carleton, 1938, p. 183.

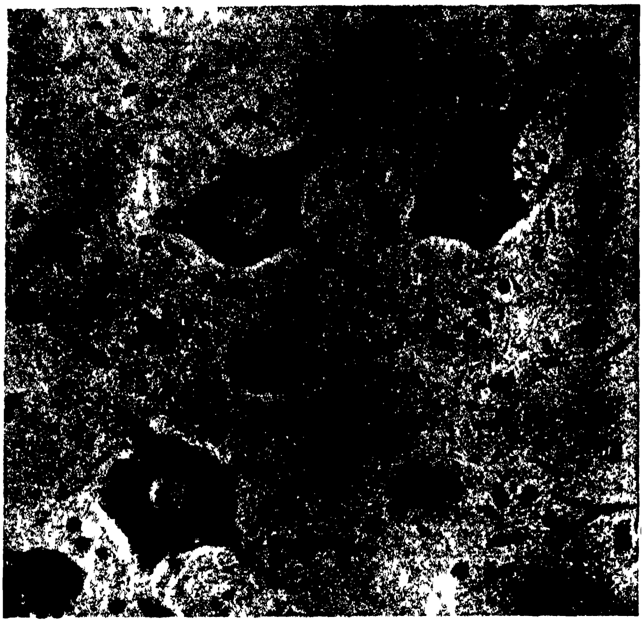

Fig. 637. *Normal motor nerve-cells of ventral horn of spinal cord* showing central position of nucleus, normal Nissl-granules, and protoplasmic processes. (For comparison with degenerated cells in Fig. 638 below.) (Nissl's method.) × 300.

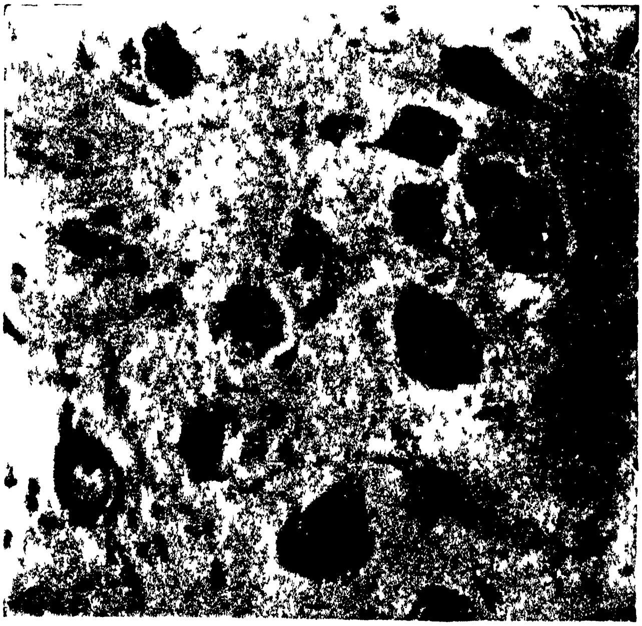

Fig. 638. *Anterior poliomyelitis* degenerated motor nerve-cells in ventral horn of cord, showing eccentric position of nucleus, and disappearance of Nissl-granules and of the protoplasmic processes. (Nissl's method.) × 300,

The **microglia-cells** (for the mesoblastic origin of which and their distribution in the nervous tissues see pp. 955-6) are concerned especially with carrying out all the varied functions characteristic of cells of the reticulo-endothelial system. In a recent paper, del Rio-Hortega [1] sums up these processes as follows : " Each of the three elements of the nervous system reacts differently in disease. The nerve cells suffer degenerative changes, the glia cells show a tendency to proliferate in cicatricial processes, while the microglia cells work intensively to take up and . . . in their cytoplasm [deal with] the products of degeneration of the other elements." In this connection he also writes : " The microglia, or third element, although it is not a part of the fundamental architecture of the central nervous system, is always present in nerve tissue ; indeed, it is intimately associated with its elements for the auxiliary, but nevertheless necessary, task of taking up, transforming and removing the products of normal metabolism and abnormal disintegration of neurones."

Inflammation of the neuraxis, according as it attacks brain or cord, may be predominantly an **encephalitis** or a **myelitis** ; or it may in varying degree be a combination of these—an **encephalo-myelitis.** Such inflammatory lesions tend to be either **generalised** or **localised** according to the nature of the irritant, its line of approach and method of attack. Some irritants have a selective affinity for certain of the tissue-elements and sometimes for the tissue-elements of some particular area or locality of the nervous system, for example, amongst others, for cortex or white matter : the corpus striatum, or even one of its component parts such as the pallidum : or the ventral horns of the spinal cord.

The majority of the more widespread varieties of encephalitis are produced by **viral infections,** some of which have a special tendency to attack the nervous system, and perhaps, as just indicated, certain portions of it. These **neurotropic-virus diseases** are described in Chapter IV, pp. 96–123, and include those associated with **variola, vaccinia** and other of the **acute infectious diseases** (p. 98 *et seq.*) ; and also the more specific virus-produced diseases :—

Acute anterior poliomyelitis and **polio-encephalitis** (p. 105).
Epidemic encephalitis (encephalitis lethargica) (p. 109).
Rabies or **hydrophobia** (p. 114).
Acute ascending myelitis (p. 116).
Acute lymphocytic choriomeningitis (pp. 116 and 1000).

It is convenient, however, to place here (pp. 1048 and 1050) several illustrations of some of these diseases which we were unable to include in Chapter IV.

ACUTE ANTERIOR POLIOMYELITIS and POLIO-ENCEPHALITIS [2] **(Infantile Paralysis).** The earlier acute inflammatory phases of this disease have been described on pp. 105 to 109. Depending upon the mildness or severity and the duration of the attack, and also upon the age of the patient and whether the tissues are still growing and are not yet fully developed, varying degrees of damage are sustained by the component elements of the cord, especially the motor neurones—with resulting trophic and degenerative changes in the muscles supplied by them. The attack is usually more or less unilateral, and may be focussed upon certain groups of motor neurones, or even on scattered individual nerve-cells, in one of the ventral horns ; but it is occasionally bilateral, though perhaps in unequal degree. The main resulting lesion is found

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[1] Pio del Rio-Hortega, (Madrid and Oxford), " The Microglia," *Lancet*, 1939, **i**, 1023, and Editorial, *ibid.*, p. 1051.

[2] Greek, πολιός, *polios*, grey, referring here to the " grey matter " of the spinal cord and brain respectively.

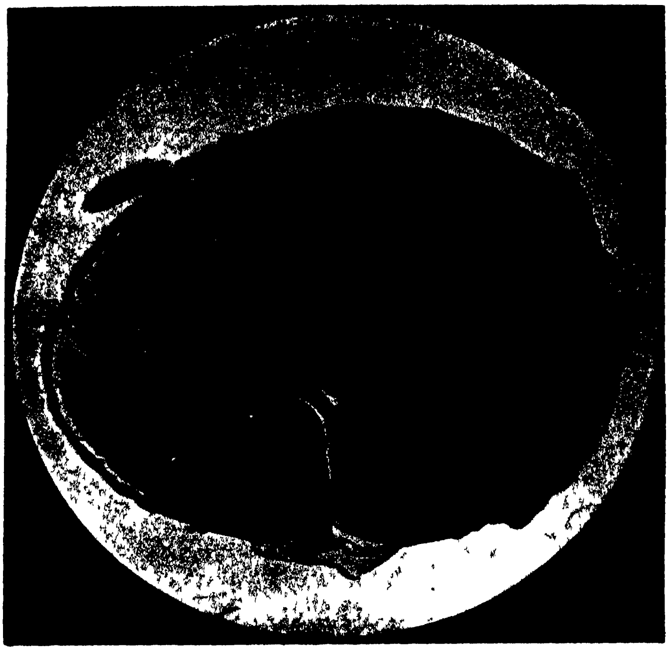

FIG. 639. *Anterior poliomyelitis:* section of cord in the cervical region from a case of old-standing infantile paralysis, showing the atrophy of one anterior horn and degenerative and sclerotic changes in the white matter in the neighbourhood. (Stained with carmine.) × 8.

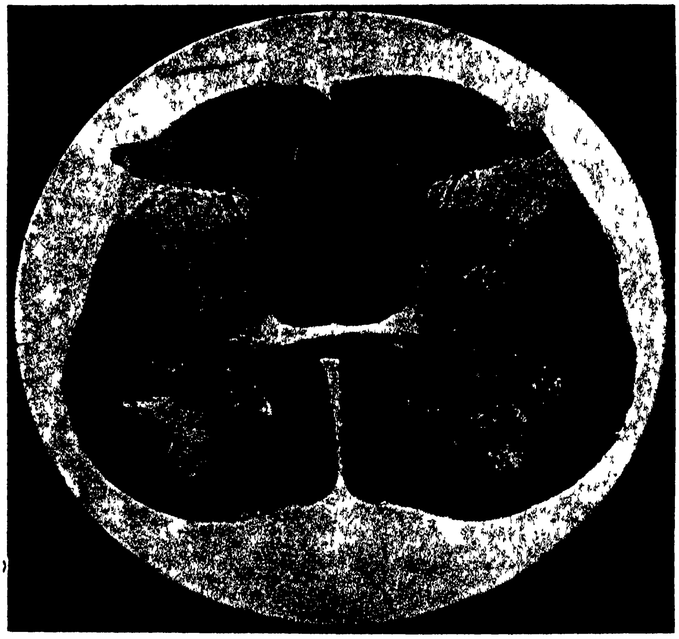

FIG. 640. *Anterior poliomyelitis:* section of the lumbar cord from an old-standing case of infantile paralysis, showing the resulting shrinkage of the affected ventral horn. Weigert-Pal method for myelin. × 8.

in the lumbar region when the paralysis affects the leg : and in the cervical region when the arm is involved, perhaps along with the diaphragm and other muscles of respiration. Part, or the whole, of the ventral horn may show degenerative changes ; in the anterior commissure, partial destruction of fibres is sometimes found ; and the ventral nerve-roots and the muscular branches of the peripheral nerves undergo atrophy.

In **old-standing cases,** the affected ventral horn, or part of it, has become smaller than that of the opposite side (Figs. 639 and 640). Motor nerve-cells—usually in diminished numbers—may still be present and apparently comparatively normal : others shrunken and degenerated. The localisation of motor functions to the various groups of nerve-cells in the ventral horn furnishes the explanation of the limitation of the paralysis to certain combinations of muscles—for a study of a series of cases proves that certain groups of cells, as we have stated, are shrunken and degenerated, whereas others are apparently uninjured. There is, usually, an increase of neuroglia, the delicate fibrils of which form a loose reticulum. The nerve-fibres are diminished in numbers and may even be almost completely absent. In some cases, the only change is in the motor-cells and the delicate nerve-fibres—the neuroglia showing little or no obvious variation from normal. The blood-vessels are sometimes thickened, and the perivascular spaces dilated. In **all cases,** there is descending degeneration of the motor-fibres associated with the affected cells ; and the muscles, the functions of which have been impaired, also undergo degeneration—the muscle-fibres becoming atrophied and occasionally replaced by fat. The other tissues, as noted on p. 109—bones, blood-vessels, etc.—share, to a greater or less degree, in this atrophy, or—more accurately—in this atrophy combined with impaired growth and development.

Wernicke's encephalopathy,[1] so named because, in 1881, the disease was originally described by him (under the name of "**polio-encephalitis hæmorrhagica superior**"), is a condition with well-defined and localised lesions in the grey matter around the third ventricle, particularly in the corpora mamillaria, and in the hypothalamus and median part of the thalamus (centres believed to be concerned with the controlling, not only of many of the vital functions of the body, but also of the mental and emotional states accompanying these), and perhaps also extending down in the grey matter around the aqueduct, sometimes as far as to the floor of the fourth ventricle. These lesions are usually symmetrical and characterised by dilatation and thickening of the capillaries, by the frequent occurrence of petechial hæmorrhages, degenerative changes in the nerve-cells and more particularly in the glia, with the presence of microglial phagocytic cells in the affected parts, and, later, by astrocytic proliferation. The association of these characteristic lesions with "Korsakow's psychosis" (a confusional mental state which is found in some alcoholic subjects, usually along with "alcoholic neuritis"—see pp. 445, 1157, 1180 and 1184), and also their occurrence in certain cases of carcinoma of the stomach and other gastric and gastro-intestinal disorders as well as in the hyperemesis of pregnancy, and sometimes in cases of macrocytic anæmia, suggests that the causation may be due to digestive disturbances, including a deficient supply or absorption of vitamins, especially, it is thought, of B_1.

Acute Ascending Paralysis (see also p. 116). In the past an "acute ascending paralysis of Landry," first described by him in 1859, has long been regarded as a clinical and pathological entity ; but, with increasing knowledge, many of the cases previously looked upon as comprising this group are now recognised as having been examples of acute anterior poliomyelitis (p. 105): acute toxic polyneuritis—itself an indefinite and heterogeneous group (pp. 1182–3): rabies or hydrophobia (pp. 114–16): as well as occurring in the course of certain of the specific infectious and infective diseases such as diphtheria: and even in acute syphilitic meningomyelitis. The various pathological lesions in the spinal cord and medulla characteristic of these may therefore be found in cases dying of what may have clinically been termed an "acute ascending paralysis," and we therefore think it advisable to adopt the view that the condition is merely symptomatic of some disease such as one of those mentioned.

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[1] "Wernicke's Encephalopathy (Polioencephalitis Hæmorrhagica Superior): its Alcoholic and Non-Alcoholic Incidence," by A. C. P. Campbell and J. H. Biggart, Edinburgh, *Jour. Path. and Bact.*, 1939, 48, 245.

Epidemic Encephalitis ("Encephalitis Lethargica" or "Sleepy Sickness"). A description of this is given in Chapter IV on Viral Diseases, pp. 109–113, but we append here an illustration (Fig. 641) of two small extravasations of blood, such as can often be seen as "petechial hæmorrhages" on cutting across the brain in the acuter stages of the disease (p. 112).

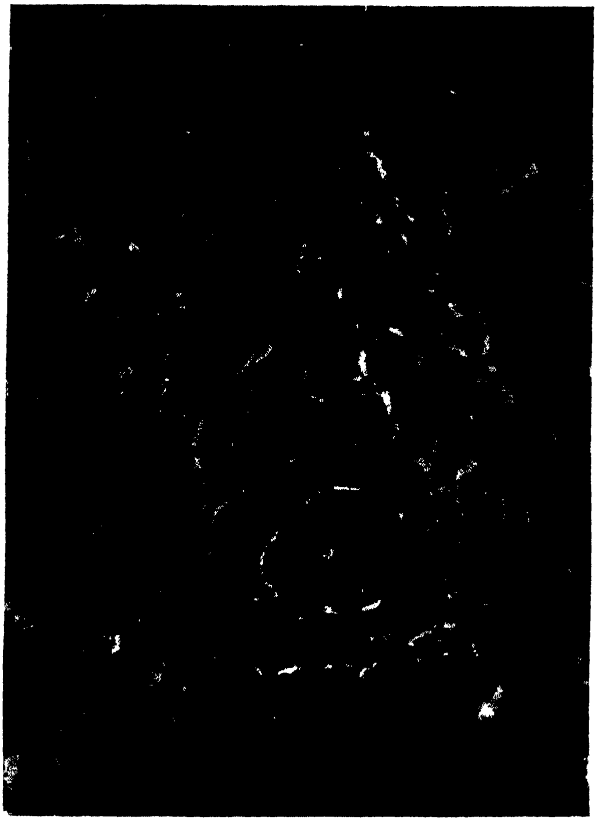


FIG. 641. *Epidemic encephalitis* or "encephalitis lethargica": section of brain showing thrombosed vessels and hæmorrhage. Hæmatoxylin and eosin. × 100.

SUPPURATIVE ENCEPHALITIS and MYELITIS, including INTRACEREBRAL ABSCESS.—Inflammatory diseases of the neuraxis produced by bacteria are **suppurative** or **non-suppurative,** the former being much the commoner. Intraventricular and meningeal suppurative infections are described on pp. 972 and 978 to 990, and in these a certain degree of involvement of the neighbouring cerebral substance may be found, though the depth to which it takes place is variable, and is sometimes less than might be expected from a naked-eye examination of the surface lesion. On the other hand, it is sometimes extensive and, as in some cases of meningococcal endoventriculitis, produces considerable purulent infiltration and softening, accompanied perhaps by hæmorrhages.

Suppurative encephalitis, however, usually takes the form of **abscess-formation.** Intracerebral abscesses are of two varieties—one due to the carriage of organisms, most commonly pyogenic cocci, to the brain by the blood-stream, for example in cases of pyæmia ; the other produced by local extension (though not invariably in direct continuity) from inflammatory foci in surrounding or neighbouring structures (p. 978 *et seq.*, and *see also* below). For the occurrence of meningitis and abscess-like cavities in the neuraxis in " torulosis," *see* p. 94.

1. **Pyæmic abscesses** are not infrequently multiple ; and, though they can occur in any part of the brain, are found rather more often in the *left* cerebral hemisphere in the area of distribution of the middle cerebral artery of that side, the latter vessel being itself the *direct* continuation of the internal carotid artery. The explanation of this appears to be that the origin of the *left* common carotid artery is from the highest part of the aortic arch, and the direction of its lumen is thus more in the same course as that of the current sweeping round the top of the arch than is that entering the innominate artery (*see also* pp. 1030–32). The infective embolic material may be derived from any of the sources which produce pyæmia (pp. 37–8 and 166) including acute septic endocarditis. Embolic abscesses in the brain are not very common, but, when they do occur, are not infrequently a secondary complication of pulmonary abscess or of suppuration in bronchiectatic or other cavities in the lung (pp. 512, 536 and 538–9).

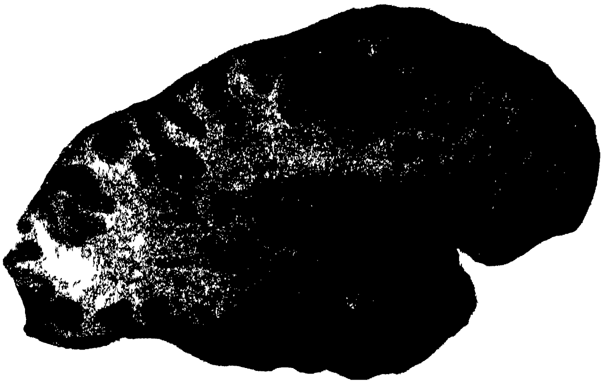
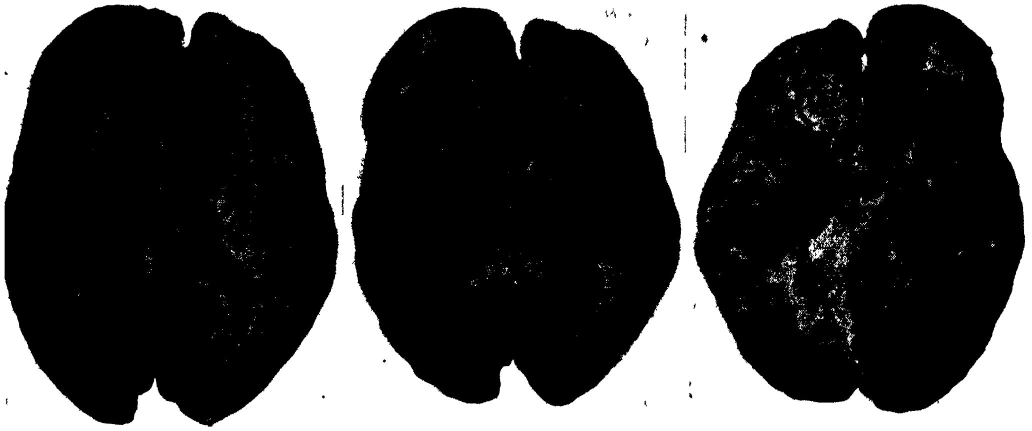


FIG. 642.—*Cerebral abscesses.* The lower abscess, in the temporal lobe, was due to direct infection through the roof of the tympanic cavity and dura in a case of suppurative disease of the middle ear.

2. **Abscesses due to direct extension from elsewhere.** The most typical examples of these are the abscesses which follow suppurative disease of the **middle ear,** and the **mastoid antrum** or **air-cells.** From the tympanic cavity the infection may spread upwards through its roof, either by way of the petro-squamous suture if, as is not uncommonly the case in the young child, it has not yet become obliterated, or directly through the tegmen tympani, with

destructive changes in the bone and the overlying dura ; and, especially if the resulting meningitis is localised by adhesions (pp. 978–9), with the production of an abscess in the **temporal lobe,** usually in its middle (Fig. 642) or posterior part. The infection may also spread by way of the small veins passing through the bone from the tympanic cavity to the superior petrosal and transverse sinuses, or into the posterior fossa through the postero-medial wall of the middle ear, with perhaps the formation of an abscess in the **cerebellum** or sometimes of a localised collection of pus in the neighbourhood of the cerebello-pontine angle. When, in middle-ear disease, abscesses develop in the above-mentioned positions with no apparent naked-eye involvement of the dura or of the bone forming the roof or walls of the tympanic cavity, the infection has taken place probably along some of the minute efferent veins.



(A) (B) (C)

FIG. 643. *Chronic cerebral abscesses following upon old-standing suppuration of the left frontal sinus,* due to infection with *Staphylococcus aureus*, in a man aged twenty-nine years. The skull had been fractured seven years previous to admission to hospital for " fits." The lumbar-puncture fluid on admission was still completely negative. An extradural abscess had formed, but without any general infection of the meninges : followed by the formation of other abscesses in the left frontal lobe, gradually extending backwards and inwards, as shown in Figs. (A) and (B), though the infection was still shut off from the general surface of the brain by the firm chronic fibrous adhesions, seen from below in Fig. (C) over the left frontal pole. The findings in the cerebrospinal fluid still remained negative , but, when the *ventricles* were reached by the infection, a rapidly-spreading suppurative *endoventriculitis* ensued, extending down the whole ventricular system and reaching the surface at the various points detailed on pp. 983–4, thus setting up an *acute "post-basal meningitis,"* which, although due to *Staphylococcus aureus, exactly simulated the distribution of a typical meningococcal case* (p. 984). (W.E.H. case.

Abscesses in the brain may originate also by direct spread **from the bone** or **dura**—an extra-dural or sub-dural abscess being first produced. If infection from this does not lead to a general suppurative meningitis, adhesions to the subjacent surface of the brain are formed and seal off the subarachnoid space laterally. The infection may, however, pass inwards through the central part of such an area and so come to involve the brain secondarily, with the production of an abscess, or sometimes a chain of intercommunicating abscesses in its substance (Fig. 643), or other abscesses may be developed at a distance (Fig. 642).

It may be noted also that localised areas of **non-suppurative** encephalitis are sometimes produced in any of the situations which are themselves liable to become the sites of intracerebral abscess and from the same causes, *e.g.*, the temporal lobe or cerebellum secondary to middle-ear infections, or adjacent to infected lesions of the frontal or ethmoidal sinuses, or in compound fracture of the skull.

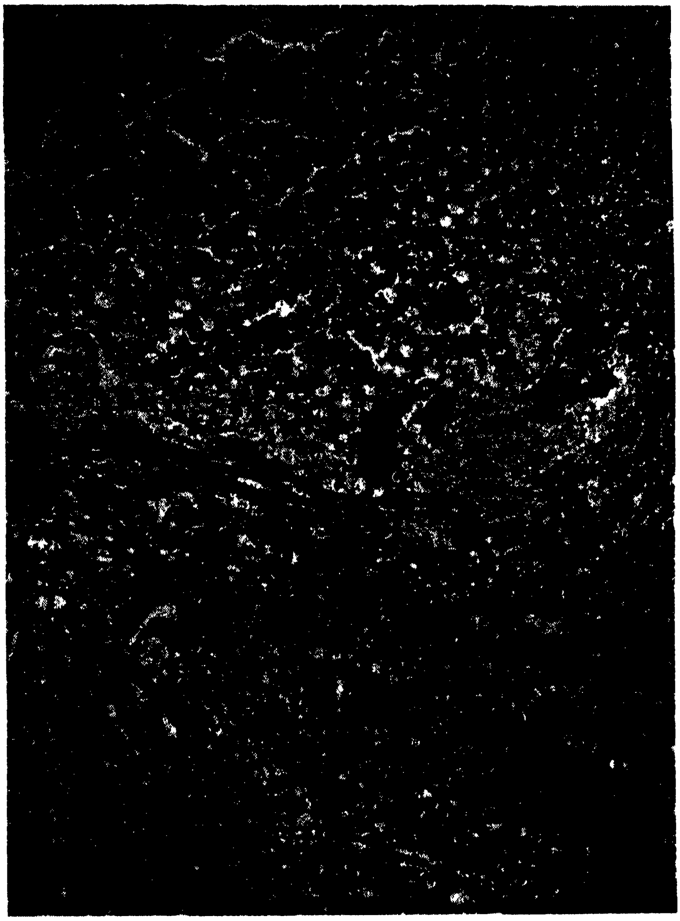


FIG. 644. *Chronic cerebral abscess*: low-power view of margin of one of the abscesses illustrated in Fig. 643, showing formation of granulation-tissue, etc. Note the aggregation of phagocytic "foam-cells," the function of which is to clear up the debris. For details, see Fig. 645 on p. 1056. Mallory's method for connective tissue. × 100.

Injuries to the head, especially compound fractures through the ear or roof of the nose or one of the paranasal sinuses, perhaps most frequently the frontal (Fig. 643), as well as the spread of infection from these regions, without fracture, or from the orbit, are not uncommon causes of cerebral abscesses.

Penetrating wounds, due to bullets or fragments of shrapnel or of high-explosive shell, with or without other foreign material carried in by them, may lead to abscess-formation, either around these foreign bodies themselves, if embedded, or along the track made by their passage. The infection so produced occasionally remains " latent " for a considerable period, symptoms of chronic abscess supervening perhaps only after an interval of several weeks or even months.

Characters of the Abscesses. In size, these intracerebral abscesses vary considerably. They are usually approximately spherical or ovoid in shape, and, in the more typical cases, for example those secondary to disease of the middle ear, the contained pus is often greenish in colour, of a thick creamy consistence, and frequently has a putrid odour, from the presence of anaerobic or other organisms which have obtained entrance to the tympanic cavity by way of the Eustachian tube from the throat, in addition to the usual strepto-, staphylo- or pneumo-cocci. These abscesses are as a rule somewhat chronic, and their walls are formed by a layer of septic granulation-tissue containing pus-cells and various types of phagocytic cell ; and in the outer part of which there is usually a layer of varying thickness consisting of proliferated connective tissue and blood-vessels, outside which again there may be a zone of proliferating glia, chiefly astrocytic in type.

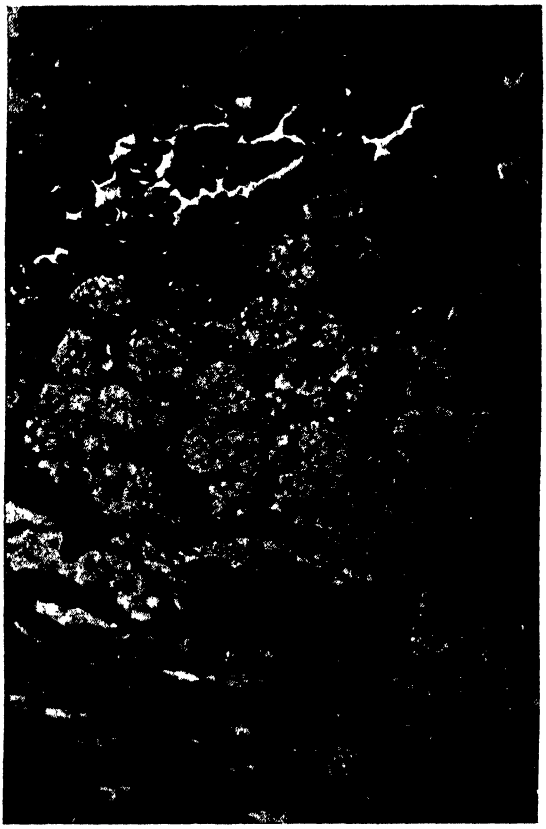


FIG. 645. *Chronic cerebral abscess :* section of periphery showing the formation of granulation-tissue, with collagenous fibres and new capillaries, together with numerous *phagocytic* "*foam-cells*" engaged in clearing up inflammatory debris. (*Cf.* the so-called "*xanthomatous reaction*" in tumours, especially meningiomas, and *see* p. 1097 and also Figs. 659 and 660, pp. 1084–5, and Fig. 749, p. 1161.) Mallory's method for connective-tissue. × 400.

The changes in the cerebrospinal fluid vary with the position of the abscess.

If this is situated **deeply** in the cerebral substance, the fluid, under increased pressure, is clear and colourless, with a slight or moderate pleocytosis up to perhaps a hundred cells or more, and a moderate increase of protein of, say, 30 to 60 mgr., together with a trace of globulin. Sugar and chlorides are, at this stage, not diminished. As is to be expected with an increased protein-finding, the colloidal-gold curve is slightly raised, but the position of the rise is variable—most commonly in the central zone. The cells are predominantly small lymphocytes, but usually with a varying proportion of polymorphs, perhaps up to some 20 or 30 per cent.

If the abscess is **near the surface,** either meningeal or ventricular, a more pronounced reaction is found—a higher cell-count with a greater proportion of polymorphs, and a more pronounced increase of coagulable protein ; but, unless the infection itself has spread to and involved the subarachnoid space or the ventricular system, microscopical and cultural examinations for bacteria are still negative. If, however, the infection comes to involve either of these surfaces, the characters of the exudate become those of a frankly purulent meningitis, with further increase of cells, especially polymorphs, turbidity, the occurrence of a fibrinous coagulum, diminution of sugar and chlorides and the presence of free complement (pp. 963–4 and 980).

The presence of a neutrophil inflammatory leucocytosis in the blood is of importance in the diagnosis of cerebral abscess, together with pyrexia and the occurrence of symptoms of an expanding intracranial lesion, and evidence of an as yet " aseptic " meningeal reaction, especially the presence of a normal amount of sugar and normal (or only slightly decreased) chlorides. An analogous finding is, however, also obtained in middle-ear, mastoid and paranasal-sinus infections which may have caused extradural suppuration or venous-sinus thrombosis, but which have not yet infected the inner surface of the dura and the leptomeninges. The condition of the fluid may return to normal on removal of the septic focus. If any of these lesions come to involve the surface of the brain, the results in the cerebrospinal fluid will simulate those produced by an intracerebral abscess, or even those of meningitis, but with a negative microscopical and cultural finding for the presence of bacteria.

Conditions resembling, but to be differentiated from, Infective Suppurative Encephalitis and Cerebral Abscess. A considerable amount of **secondary softening** of the tissues of the brain or cord frequently supervenes in or around the immediate neighbourhood of lesions such as **hæmorrhage** or **tumour,** and is sometimes referred to as an " encephalitis " or a " myelitis," but it is preferable not to employ these terms unless the lesion is actually inflammatory in nature, as may be the case, for example, round an abscess.

A pronounced degree of **polymorphonuclear infiltration** is often found **in and around cerebral tumours** in which **necrosis** or **hæmorrhage** has occurred, and, when involving the surface of the brain (a phenomenon seen perhaps more frequently in the frontal region than elsewhere), may produce in the cerebrospinal fluid a picture simulating cerebral abscess or even meningitis. Thus the presence of polymorphs in the fluid does *not* of itself in the case of some tumours serve to differentiate this reaction from that around a cerebral abscess. Both of these types of lesion may, however, in ordinary circumstances be distinguished from a bacterial meningitis by the absence of organisms in the fluid and little or no diminution in the amounts of sugar and chlorides.

Reaction to Diathermy. The explanation of another phenomenon which may lead to a mistaken diagnosis of cerebral abscess or suppurative infiltration is the rapidity with which polymorphonuclear leucocytes emigrate from the damaged vessels, even during the course of an operation, when the surgeon employs the **diathermy-knife or -needle** (*cf.* p. 35). The "cooking" of the neighbouring tissues, as well as the thermal damage to the walls of arterioles, capillaries and venules themselves, **stimulates active leucocyte-emigration,** and, unless the observer is familiar with this phenomenon, he may, especially when working with fresh-wet biopsy material, as well as with sections, easily be misled into making the diagnosis of an acute suppurative inflammatory lesion (**Fig. 646**). A pronounced degree of this polymorphonuclear infiltration, as well as the crowding of neighbouring blood-vessels with leucocytes, can take place in the

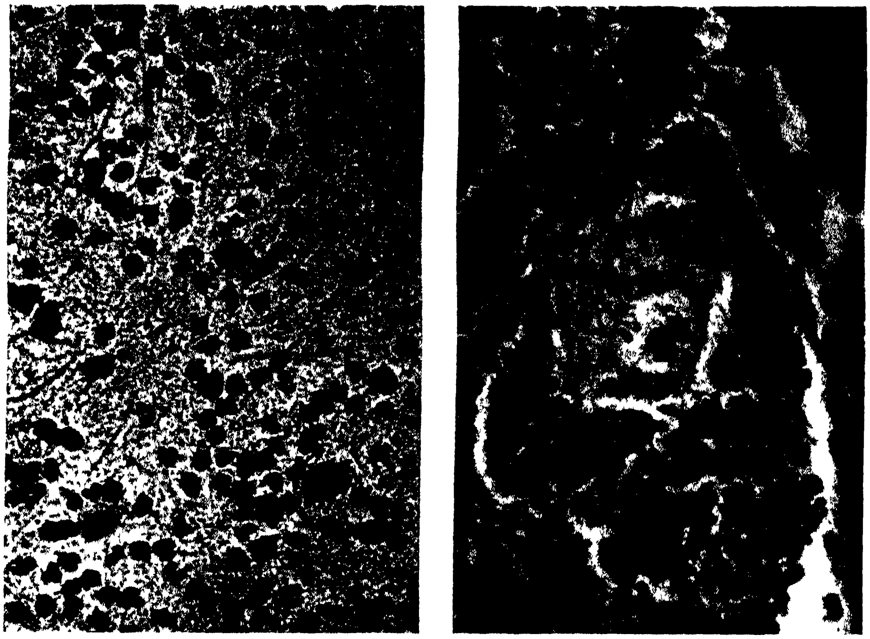

(A) (B)

FIG. 646. *Rapid polymorphonuclear reaction resulting from the use of the electro-cautery during operations.* These photomicrographs are from biopsy-specimens of *normal* brain-tissue removed by Mr. Geoffrey Knight during exploratory operations.

(A) *Fresh wet toluidin-blue preparation* showing otherwise normal tissue of white matter of frontal lobe crowded with polymorphs. (From female, aged thirty-three years.)

(B) *Paraffin section* of surface of temporal lobe showing "cooking" of the leptomeninges and subjacent cortex. Except for the recent operative hæmorrhage and these patches of polymorph-emigration, there was no pathological lesion in the immediate neighbourhood. (From female aged twenty-two years.) (Hæmatoxylin and eosin.) (W.E.H. cases.) × 400.

operation-area within fifteen or twenty minutes of the opening of the head during, say, a craniotomy for cerebral tumour.[1]

The injection of certain radio-opaque substances, for example, " thorotrast," **into the cerebral ventricles,** especially if it leaks into the brain-substance, more particularly in elderly patients, sometimes leads to a pronounced polymorph reaction, indistinguishable from " suppuration " (pp. 972–3). A similar unfortunate result may also follow the diagnostic injection of such substances **into the blood-vessels** of the brain, in, say, a case suspected of being one of cerebral aneurysm (see also first footnote on p. 1042), where the lesion proves in reality to be, perhaps, a breaking-down tumour, or if, when an aneurysm *is* present, it has become thrombosed or is leaking ; in which case extensive softening of neighbouring brain-tissue may follow. In this connection it may be noted that this " aseptic suppurative reaction " and consequent myelomalacia (p. 1167) may follow the injection of some radio-opaque substances **into the spinal theca.** We have ourselves observed this after the intrathecal injection of " thorotrast " and also of oily preparations of iodine, especially if the latter substance has been too concentrated or if any considerable amount of the material injected remains unremoved or unabsorbed.

Actinomycotic and also rarer forms of **streptothricial abscesses** occur, and are usually secondary to abscesses caused by these organisms in the lung or elsewhere (pp. 91–3 and 568A).

DISSEMINATED SCLEROSIS (*synonyms* : **Multiple** or **Insular Sclerosis**) is one of the commoner of the important forms of nervous disease. Of still unknown ætiology, it is characterised by the occurrence of **patches of demyelination,** irregular in size, shape, acuteness or chronicity, and distribution ; and is followed by sclerosis. It can attack practically any part of the white and grey matter, but particularly the white matter, of the brain and spinal cord, as well as the optic nerves—and less frequently the chiasma or tracts—**eye-trouble,** most commonly but not invariably unilateral, due to retrobulbar neuritis, being often the earliest symptom to call the patient's attention to his disability. The disease attacks males oftener than females, in the ratio of about three to two ; and the age-incidence is mainly between twenty and forty years, the condition being rare, though not unknown, in children, in whom it practically always takes the form of retrobulbar neuritis. Its actual onset is uncommon in old persons, and, if elderly patients come under observation for the disease for the first time, the history of some antecedent attack with "nervous " symptoms, most commonly "eye-trouble," several or perhaps many years previously, can often be elicited.

The onset varies greatly in acuteness and severity. It is often insidious, eye-symptoms, pointing to retrobulbar optic neuritis, being, as we have just noted, perhaps the commonest early evidence of its presence, accompanied or followed by sensory disturbances, impairment of speech, and varying degrees of tremor (especially so-called "intention tremor") and spastic paralysis, the clinical picture, like the distribution of the lesions themselves in the nervous system, being extremely varied in character and degree. Wilfred Harris (*see* footnote on pp. 1183–4) calls attention to the liability of patients, especially women, suffering from disseminated sclerosis, to neuralgic attacks of trigeminal tic.

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[1] These observations and, as noted on p. 950, much of the work upon which the descriptions in this chapter on the Nervous System have been based are part of unpublished research-work carried out in the Pathological Department of the West End Hospital for Diseases of the Nervous System, London, made possible by grants from the Medical Research Council to one of the authors (W. E. C. D.). In 1939, these investigations were interrupted by the War. (*See* also our Preface, and the Preliminary Note to this Chapter on p. 950.)

Whether the characteristic patches in the brain and cord are brought about by a demyelinating encephalomyelitis of infective origin due to a virus : or, as some believe, to a spirochæte, or by some other as yet unrecognised agent : or whether it is a degenerative deficiency-disease like pellagra or beri-beri, is still unknown, although analogy and indirect evidence might be thought to be in favour of the likelihood of an infective agent as causal. The disease is not usually regarded as having any hereditary or familial element in its production, although, occasionally, several cases may occur in one family.

A notable feature of disseminated sclerosis, and one to be borne in mind when attempting to assess the value or otherwise of the many suggested therapeutic measures, is the tendency, quite apart from any treatment, to the occurrence of **remissions,** often of considerable duration, but with subsequent **relapses. Recent** and **older patches**, therefore, are often found occurring side by side in the brain and cord of patients who die during a relapse ; and the stages of the process can be traced, from the softer yellowish patch in which beaded and fragmenting **myelin** is still present within the irregularly swollen nerve-sheaths, to those in which it has been freed and is being taken up by the mobilised microglial foam-cells which thus become laden with the degenerated myelin and its products. The **axis-cylinders**, though showing a certain degree of irregular swelling, do not suffer to the same extent as their myelin-sheaths, and the naked fibrils running through the patches often persist in considerable numbers, thus accounting for the possibility of partial recovery of function frequently noted during remissions. This process of **demyelination** and removal of the degenerated myelin by phagocytes gradually becomes more complete, and is accompanied and followed by a **progressive gliosis** in which more particularly

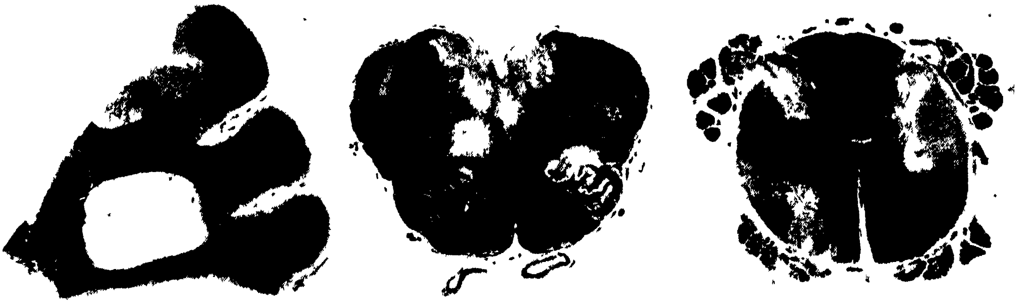
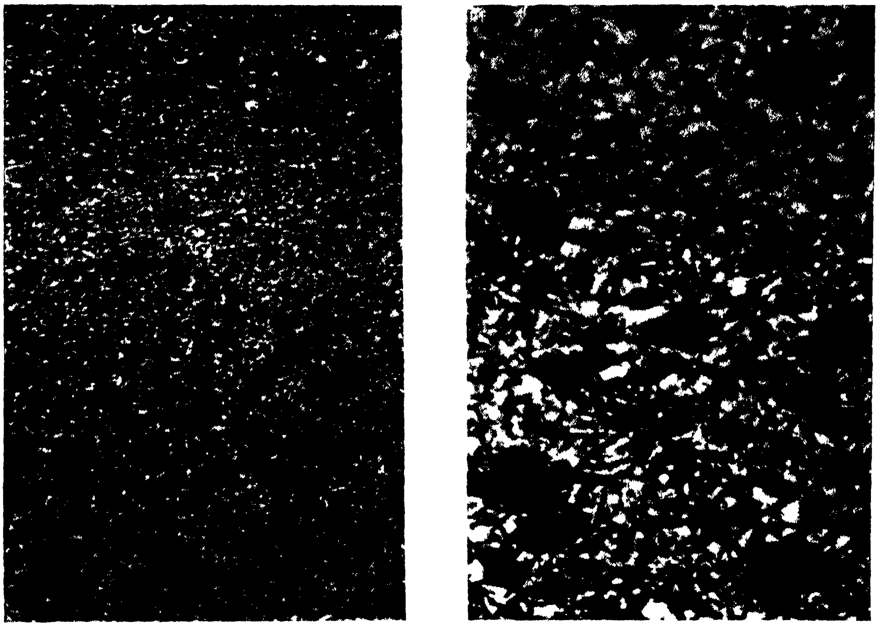

(A) × 1. (B) × 2. (C) × 4.

FIG. 647. *Disseminated sclerosis* in a man aged thirty-four years : series of sections of (A) right frontal lobe : (B) medulla oblongata at level of olivary nucleus : and (C) lumbar enlargement of cord—to illustrate the irregular size, shape and distribution of the patches of demyelination. From these, the varied nature of the symptoms in any given case will be understood : for example, involvement in (A) of fibres from the right middle frontal and pre-central gyri : in (B) of various cranial-nerve nuclei in floor of fourth ventricle, etc. : and in (C) of right dorsal horn, and right cortico-spinal tract, and smaller patches on opposite side of cord. Weigert-Pal method for myelin. (W.E.H. case.)

the astrocytes take part. Thus come to be formed the firm dull-grey or greyish-red slightly translucent patches or "plaques" of what is practically dense glial scar-tissue, through which, however, as noted, axis-cylinders can often still be traced in considerable numbers. Similarly, when the process attacks **grey matter**, many of the individual nerve-cells also escape destruction. A noteworthy feature is that the margins of the patches are sharply defined, with sudden transition from comparatively normal myelinated fibres to completely demyelinated tissue, a phenomenon well brought out in sections stained by the Weigert-Pal method (Figs. 647 and 649). The patches vary in size from a few millimetres up to several centimetres in diameter.



(A) × 100. (B) × 400.

FIG. 648. *Disseminated sclerosis*: (A) low-power view near edge of a demyelinated subcortical patch smaller and more chronic than that shown in Fig. 647 (A), stained to demonstrate the gliosis which is now pronounced, with proliferation of astrocytes and a dense felted glial background. (B) High-power view of the same, showing the astrocytes and glial groundwork. Mallory's connective-tissue stain.

Unlike some of the demyelinating diseases of known infective nature, *e.g.*, produced by filter-passing viruses, the lesions of disseminated sclerosis do not have any distinctive peri-arterial distribution, nor do the capillaries or arterioles themselves show special pathological changes. It has been thought by some, however, that there is a tendency for the patches to be found in the immediate vicinity of the ventricles or to be in the drainage-areas of veins.

The examination of the **cerebrospinal fluid** is of importance in the diagnosis of disseminated sclerosis. Except when the disease is inactive, the picture is, in more than half the cases, a fairly characteristic one, with, especially during the onset or during a relapse, a monocytic pleocytosis (mainly of small lymphocytes with occasional small endothelial cells) moderate in degree, often under 10 cells, sometimes 10 to 50, and seldom as many as 100 or more per c.mm.

Total protein usually shows a mild increase, 35 to 40 up to 60 or 70 mgr., and rarely 100 mgr. or more. A faint trace of globulin accompanying a total protein of as low perhaps as 30 mgr. is of importance as a diagnostic point, but the most valuable finding, taken along with negative Wassermann and Meinicke clarification reactions, is the occurrence, in a considerable proportion of cases, of a first-zone (" paretic ") or, less frequently, a mid-zone, Lange's colloidal-gold curve. Sugar and chlorides usually remain normal, and the pressure may be slightly raised, but does not rise above 200 mm.

Disseminated Myelitis with Optic Neuritis (" Neuromyelitis Optica " of Devic) is a form of acute or subacute disseminated encephalo-myelitis or encephalo-myelomalacia accompanied by bilateral optic neuritis. Some doubt has recently been expressed as to whether this is a definite nosological or pathological entity, or is merely a heterogeneous group of cases in which the optic nerves and spinal cord happen to be singled out for attack by processes allied or analogous to those of disseminated sclerosis, diffuse cerebral sclerosis (Schilder's "encephalitis") or some similar condition. In what are regarded as typical instances of "neuromyelitis optica," there is patchy demyelination in cerebrum, optic nerves and spinal cord—more particularly in the **cord**—but *not*, it is said, in the cerebellum. In the cerebral hemispheres, the lesions are found mostly in the white matter and, like those of Schilder's disease, tend to spare the subcortical arcuate fibres (pp. 1063–5 and Figs. 650–1). The special feature which has been thought to differentiate "neuromyelitis optica" from these other diseases is a tendency to the occurrence of **softening** and **cavitation,** sometimes extensive, in the areas of demyelination in the brain and more particularly in the cord. Persons of any age are attacked, but, unlike disseminated sclerosis, the disease is found especially in children, and death may result from the extensive myelomalacia. Further investigation is necessary before an opinion can be given as to the nature of the disease.

FIG. 649. *Disseminated sclerosis :* low-power view of edge of small patch in right olivary nucleus shown in Fig. 647 (B), to illustrate sudden transition from myelinated to demyelinated tissue. Weigert-Pal method for myelin. × 100.

Owing to the cerebrospinal fluid having been examined in as yet comparatively few cases, the typical picture is not fully established. In a case thought to be a typical example of the condition,[1] investigated by one of the authors during its acute phase, the colloidal gold-curve was 5554321000, *i.e.*, of first-zone or " paretic " type (p. 964), with only a minor degree of lymphocytic increase (4 to 8 per c.mm.) and the faintest detectable trace of globulin, associated with a slight increase of total protein. The subsequent course of certain of these cases believed originally to have been " neuromyelitis optica " has led to the diagnosis being changed to that of disseminated sclerosis.

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[1] " Neuromyelitis Optica " by C. Worster-Drought, *Post-Graduate Medical Journal,* London, May, 1936, p. 198.

DIFFUSE CEREBRAL SCLEROSIS. (*Synonyms :* Schilder's " **Encephalitis Periaxialis Diffusa,**" or **Progressive Degenerative Subcortical Encephalopathy.**) This heredo-familial disease is characterised by widespread demyelination of the white matter of the cerebral hemispheres, and was described first by Schilder in 1912 as an " encephalitis." The nature of its causation, whether

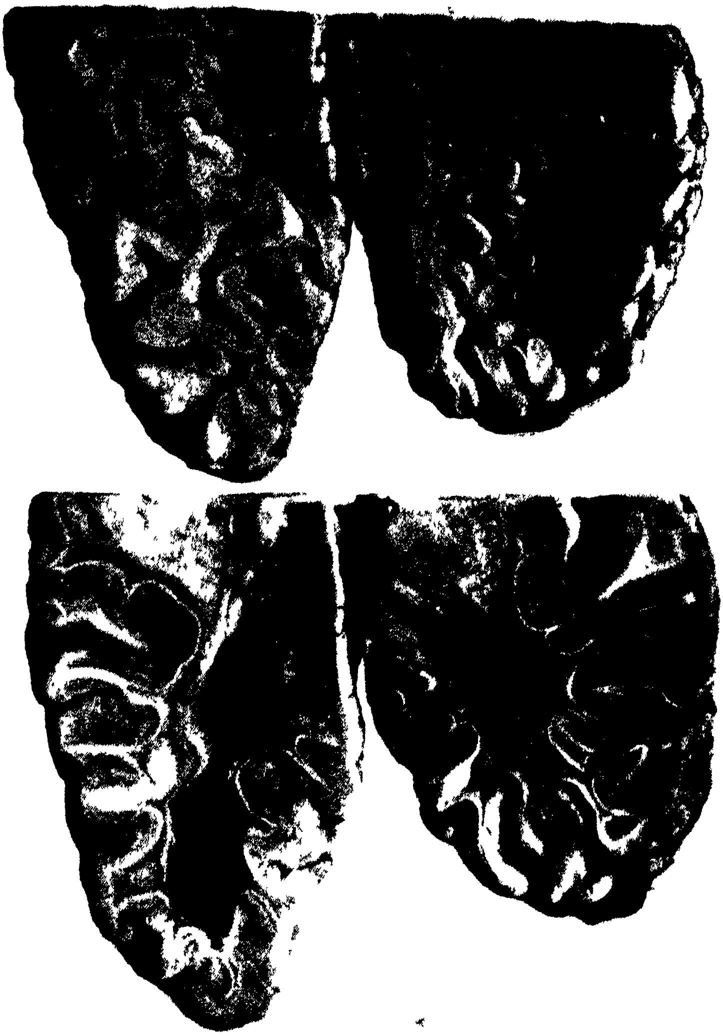

Fig. 650. *Diffuse cerebral sclerosis* or " *encephalitis periaxialis diffusa* " of *Schilder,* in a girl, one of a family of five, of whom three other sisters did, and an only brother, aged ten years, did not, suffer from the disease. Horizontal section through occipital poles, showing extreme atrophy and contraction of the white matter—practically to the vanishing point on the left side posteriorly, between the dilated ventricle and the cortex, accounting for the progressive cortical blindness from which the patient suffered. Note the " white line " of the less affected subcortical layer. (E. D. Macnamara and Carnegie Dickson's case, W.E.H.[1])

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[1] *Proc. Roy. Soc. Med.*, 1932–33, 26, 297.

degenerative, neoplastic, or infective and inflammatory, or due to some deficiency-factor or factors, is still unknown, and we therefore prefer meantime to use the non-committal term " sclerosis " for the condition, although the word " encephalopathy " shares with it the same dubious advantage of having no specific significance. It is a disease mainly of childhood, but patients of any age and either sex may be attacked. Acute cases, fatal perhaps within a fortnight of onset, have been recorded, but are rare. The disease tends to be subacute, or slowly progressive and chronic, lasting for one or two, more rarely for as long as ten years or more, with the development

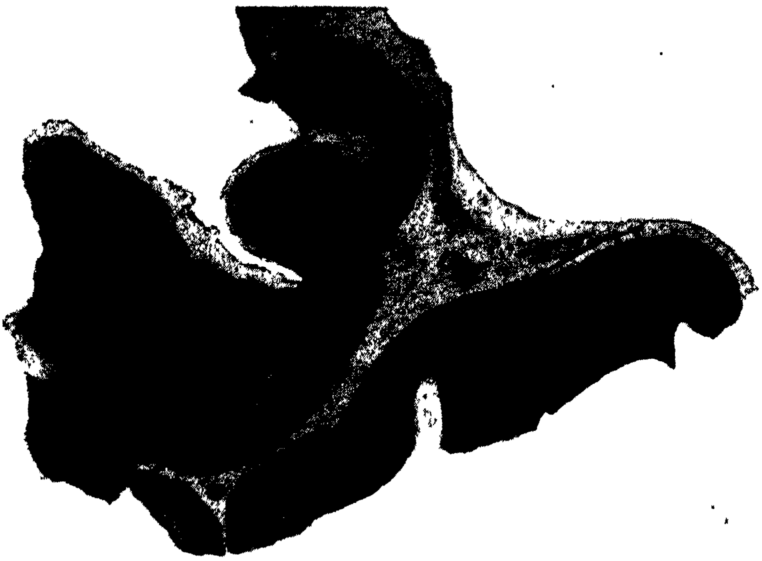

FIG. 651. *Diffuse cerebral sclerosis* (or *encephalitis periaxialis diffusa* of *Schilder*). Very slightly magnified horizontal section through left occipital pole showing extreme demyelination, degeneration and contraction of the white matter in the region of the optic radiation (compare with lower left naked-eye illustration of this area in Fig. 650). There is still a well-marked surviving subcortical zone, the black corresponding to the white line in Fig. 650. The wall of the posterior horn of the lateral ventricle is seen here as the upper right curved margin of the section. Weigert-Pal method for myelin. × 4.

of bilateral spastic paraplegia : blindness of " cortical " type, from involvement of the optic radiations at the occipital poles (Fig. 650) : deafness, when the temporal lobes become involved : and, finally, complete dementia and decerebrate rigidity. The progressive demyelination of the cerebral white matter, with, at first, swelling of the tissue, and mobilisation and proliferation of microglia-cells to become fat-laden phagocytes, is usually most advanced towards the occipital poles, thus coming to involve, as just noted, especially the optic radiations. Except for the remarkable peculiarity that it tends to spare a narrow band or zone of white matter immediately beneath the cortex, corresponding to the arcuate fibres (Figs. 650–1), this widespread destructive and degenerative process gradually spreads throughout the centrum ovale.

These changes involve the myelin-sheaths of the nerve-fibres in greater degree than the axons themselves—hence Schilder's term "periaxial" (*i.e.*, periaxonal) for the disorder—and are accompanied and followed by a gradual and progressive diffuse gliosis. This causes shrinkage in the size of the whole brain, which becomes rubber-like in consistence; and, from the sclerotic contraction, irregular dilatation of the ventricles is produced.

The findings in the cerebrospinal fluid resemble those of disseminated sclerosis, *i.e.*, a mild mononuclear pleocytosis, moderate increase of total protein, and, perhaps either a first or a mid-zone Lange's colloidal-gold curve.

An analogous condition of demyelination, but tending to attack the white matter in concentric and alternating circles or spheres, is known as the **Encephalitis Periaxialis Concentrica** of Balo (1928). J. G. Greenfield (1933) has described a progressive cerebral sclerosis in two young children, in whom the demyelination attacked those fibres which are myelinated comparatively late in development and which he attributed to deficient functioning of the oligodendroglia presiding over the process of myelination. Various other rare heredo-familial varieties of cerebral sclerosis have also been described, for example an acute infantile form recorded by Krabbe (1916); the chronic and slowly progressive infantile form of Pelizæus (1885) and Merzbacher (1910); and the subacute juvenile form of Scholz (1925). For descriptions of these, reference should be made to special works on Neurology.[1]

SECTION IX

CONGENITAL AND DEVELOPMENTAL ABNORMALITIES OF THE NEURAXIS

Gross morphological abnormalities of the brain and spinal cord are seen principally in imperfectly developed fœtuses and are interesting from an anatomical, rather than from a pathological, point of view. In the following series of such abnormalities, of which only brief mention need be made, we are considering **primary** and **congenital lesions,** and are not at present concerned with conditions such as local atrophy following secondarily upon vascular and other disease.

The brain may be congenitally deficient or absent (**anencephaly**), and this may be associated with absence of part, or the whole, of the cranial vault (**hemicrania** [2] and **acrania**), imperfect closure of the skull along the middle line (**cranioschisis**) and perhaps also with non-closure of the spinal canal (**rachischisis,** p. 1066). In conjunction with imperfect development of the skull, hernia of the membranes (**meningocele**), hernia of the brain [3] (**encephalocele**), or a combination of these (**meningo-encephalocele**) may occur. The **meningocele** consists of a protrusion of part of the cerebral membranes. In **encephalocele** there is protrusion of a portion of the brain itself. These anomalies are found most commonly in the middle line, especially posteriorly between the two lateral halves of the occipital bone: in the fronto-nasal suture: and, more rarely, in the lambdoidal, sagittal, and other sutures. They have been described as occurring also through normal and abnormal fissures at the base of the skull and into the orbit, nose and mouth.

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[1] For example, "Diseases of the Nervous System in Infancy, Childhood and Adolescence," by Frank R. Ford, of Johns Hopkins University (Baillière, Tindall & Cox, London), 1937, Chapter IV, p. 241 *et seq.*, in which the problems of the nature and classification of these and similar diseases are discussed and references to the original papers given.

[2] The term "hemicrania" has also sometimes been applied to the unilateral paroxysmal headache of migraine.

[3] **Herniation of brain-tissue,** sometimes extensive, may occur also as a result of non-congenital deficiencies in the bony wall produced by **accident** or **operation** (Figs. 688 and 705, pp. 1104 and 1118) especially if associated with raised intracranial pressure. In certain cases of prolonged increase of intracranial tension, **multiple minute herniations** of brain-tissue may be produced and simulate, but are softer than, Pacchionian bodies. They are found in similar or analogous positions to these—and are sometimes even combined with the arachnoid granulations—such hernial protrusions being pushed through small openings in the dura and producing corresponding pitting of the inner table of the bones of the skull.

SPINA BIFIDA or **RACHISCHISIS.** In this variety of congenital malformation —a form of "**Status Dysraphicus**"[1]—the development of the neural arches of certain of the vertebræ, together with the ligaments and muscles related to them, is incomplete in varying degree; and through the resulting gap the membranes or the membranes and cord may present themselves in one of several ways, as indicated in the accompanying series of diagrams.[2]

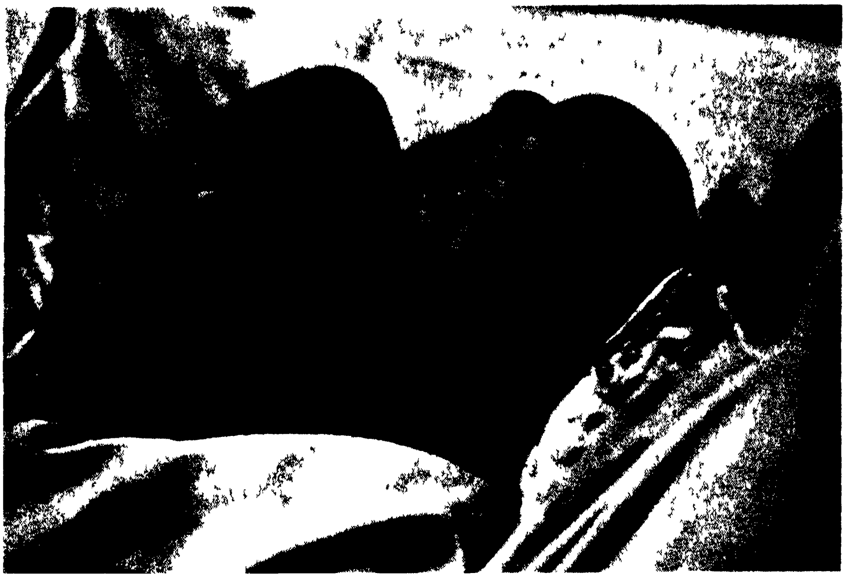

FIG. 652. *Enormous encephalomeningocele*—larger than the rest of the child's head—in a male infant, aged five weeks, which did not survive its surgical removal. (W.E.H. case.)

A. **CLOSED SPINA BIFIDA.** There may be, projecting from the back, a rounded and sometimes balloon-like swelling, situated most frequently in the lumbo-sacral region. The mass is covered with skin over the greater part of its surface, but often, towards the centre, the covering is completed by a membrane from which the skin-elements are absent. Beneath the surface integument are the membranes of the cord, or, less frequently, the arachnoid alone—the dura being sometimes deficient or absent. Such a **spinal meningocele** forms a hernial sac, at times with a comparatively narrow neck, the accumulation of cerebrospinal fluid within it being situated in the dilated and bulging theca, but with no actual nerve-tissue in the swelling.

In a **meningomyelocele,** the sac is usually sessile, and projects through a considerable gap in the neural arches, generally of several—perhaps three or four—vertebræ. The fluid in this variety has accumulated in the arachnoid space anterior, *i.e.*, deep or ventral, to the cord, and the projecting sac of dilated membranes contains both nerve-tissue and fluid, the nature of the former varying with the level of the lesion, and consisting of spinal cord or its filum terminale, nerve-roots, or combinations of these. This form is said to be, in living children at all events, the commonest of these abnormalities, the protruded cord and its nerve-roots being incorporated in the posterior (dorsal) wall of the sac, which is lined anteriorly and laterally by arachnoid, and posteriorly, *i.e.*, in the interior of the projecting wall, by pia over the nerve-tissue. At the centre of the external surface there is sometimes, in this form, a dimple corresponding to the site of an adhesion of the subjacent expanded cord or cauda equina to the inner surface of the sac ; and the centre of this dimple occasionally contains an opening which communicates directly with the central canal of the cord.

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[1] "Dysraphicus," *see* second footnote on p. 1163. "Rachischisis," from ῥάχις, *rachis* (*rhachis*), the spine or backbone, originally, a rough jagged projecting ridge: and σχίσις, *schisis*, cleavage or division—here non-union—from σχίζειν, *schizein*, to cut or divide (*cf.* Latin *scindo*, to split or divide).

[2] These diagrams were, along with others, destroyed in the Fire of the City of London on Sunday, 29th December, 1940.

In **syringomyelocele** (or **myelocystocele**), the spinal cord is spread out and thinned by the distension of its central canal from within by cerebrospinal fluid, the sac being composed of a thin layer of nervous tissue adherent to the interior of the bulging membranes. Mechanical interference with the nerve-roots as they pass circuitously round the interior of the sac to re-enter the canal and reach their appropriate intervertebral foramina, is apt to cause secondary trophic disturbances in the tissues which they supply, with perhaps necrosis and ulceration.

Spina Bifida Occulta is one of the less serious varieties of the deformity, in which there is merely some slight central deficiency of the neural arch of perhaps only a single vertebra, without protrusion of the contents of the vertebral canal, but with the presence, it may be, of merely a fibrous-tissue connection between the dura and integuments. This, however, is a condition of minor importance unless along with it there is, as occasionally happens, either outside or inside the vertebral canal, an associated **tumour**, usually lipomatous (p. 1096), but sometimes presenting on the skin-surface a hairy or vascular nævoid growth. Such tumours may remain latent for a considerable period, but may at some subsequent period take on more active growth.

Any of the foregoing types of spina bifida may be associated with other congenital malformations such as hydrocephalus, club-foot or, less commonly, pes cavus, dislocation of the hip, cleft-palate or hare-lip. When accompanied by anencephaly, the fœtus is non-viable.

B. **OPEN SPINA BIFIDA.** The formation of a **myelocele** is due to failure of the primitive lateral folds of the neural groove to unite posteriorly to form a closed canal. The lesion is situated most commonly in the lumbar or lumbo-sacral region, where the development both of the integuments and of the medullary canal has not been completed in the middle line. This form of spina bifida, therefore, consists of a cleft or groove leading down to the **interior** of the spinal canal, and there is sometimes a considerable raw surface formed by the spread-out tissues of the interior of the cord, the dorsal part of which, as well as the membranes, neural arches and skin, are absent. The condition, if the child is not already stillborn, is not compatible with life for more than a few days.

Associated with deficiency of the anterior part of the fore-brain, a single central eye **cyclopia,** is sometimes found. **Micrencephaly** or smallness of the **brain,** itself usually the cause which has led to **microcephaly,** or smallness of the **head** (the two terms are not synonymous and should therefore *not* be used indiscriminately—*see* p. 1201) may be present

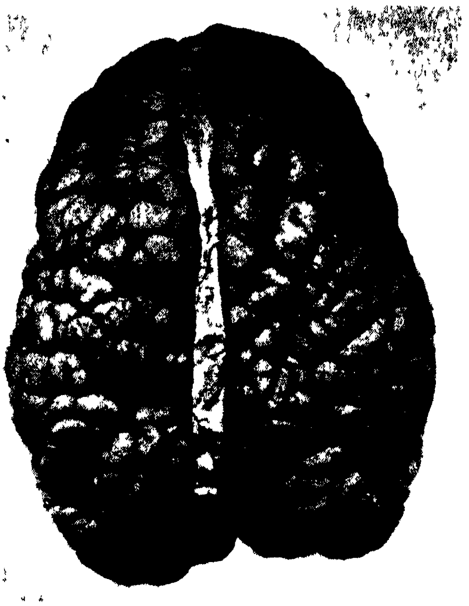

FIG. 653. *Micrencephaly with microgyria* in a mentally-defective male child of three-and-a-half years. (W.E.H.)

as congenital abnormalities, associated, it may be, with varying degrees of mental deficiency. Micrencephaly is characterised by **microgyria** or imperfect development of the gyri and sulci, these often being small, irregular in arrangement, and imperfectly formed. Though such microgyria is due usually to defective development, it sometimes results

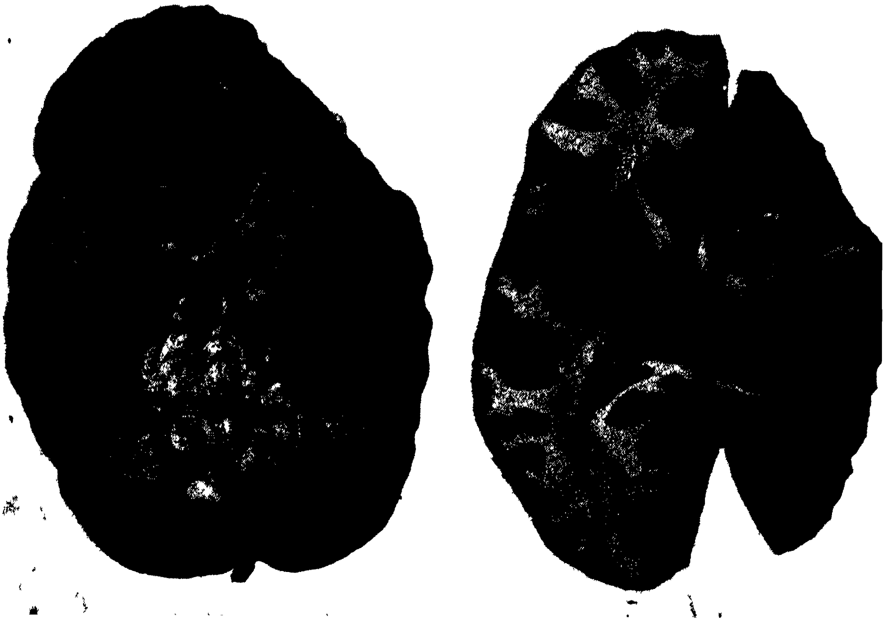

FIG. 654. *Porencephaly* of the left cerebral hemisphere, affecting especially the frontal lobe, in a male congenital epileptic idiot aged thirty-three years. (Dr. McMenemey's case.)

from some definite pathological condition in the fœtus. Thus thickenings of the pia-mater, suggesting a previous inflammatory process, have been found associated with it.

Parts of the brain are sometimes congenitally small in size or even absent, a condition known as **agenesia,** partial or complete. This is sometimes localised to certain areas in the cortex where the convolutions have been imperfectly developed, as the condition of **porencephaly**;[1] or, again, the cerebral or cerebellar hemispheres may be asymmetrical, or the whole cerebellum may be small and imperfect. The corpus callosum is occasionally absent.

CONGENITAL HEREDO-FAMILIAL AND OTHER SYNDROMES AFFECTING THE NERVOUS SYSTEM

The foregoing gross abnormalities are obviously "innate" in character, that is to say they are already present or inherent in the body at birth; but, as explained above, it is convenient to speak also of certain other conditions as "congenital" or as "hereditary," even when these terms are perhaps not applicable with strict accuracy. Many of the developmental abnormalities of the central nervous system are found amongst members of the *same* family and perhaps, in certain instances, mainly or even exclusively in siblings—blood-relations, especially children of the same parents, or perhaps of the same grandparents, *i.e.*, members of the *same* generation of that family. Though the ancestry of these patients may have been in some degree neuropathic, the parents may not themselves necessarily have suffered from the particular disease in question, and the nature of this in their offspring is therefore apparently Mendelian recessive in character. When the incidence of certain pathological conditions is thus found among siblings of the same generation, and is not an "ascending" one, *i.e.*, not amongst parents or more remote ancestors, it is permissible to describe the abnormalities present as being "**heredo-familial.**"

The ætiology of these abnormalities is in most instances still obscure, as is also their ultimate pathological nature, but it is not improbable that the methods of research and the discoveries of modern experimental embryology may throw light upon and perhaps even explain some of them (p. 291 *et seq.*). This is likely to be true especially of those conditions described as "**syndromes,**"[2] in which a number of allied, or in some instances apparently dissimilar, organs and tissues are the seat of these anomalies; or the anomalies themselves may be multiple. Such abnormality may, as stated above, take the form of arrest of development, with **agenesia** or **abiotrophy** (Gowers), total or partial, of some organ or portion of an organ, or of some particular tissue-element; or, if development continues, it does so in some perverted manner, and for this the term "**dysbiotrophy**" (suggested by Parkes Weber) is convenient. The complete series of different types of lesion which collectively go to build up a syndrome-disease may all occur together in a "typical" case; whilst in a brother or a sister or cousin, a lesser number or perhaps only one of these "units" may be found. Such partial or incomplete examples have by French writers been termed "*formes frustes.*" Moreover, one particular and outstanding element of a syndrome, or the symptoms produced by it, may so dominate the clinical picture as completely to override and obscure the others; or, again, more than one of these syndrome-diseases may be present simultaneously in the patient and, in whole or in part, the lesions characteristic of each may overlap or intermingle, and so produce complicated intermediate and mixed forms.

In connection with this series of malformations and anomalies which affect the detailed structure and architecture of the nervous tissues themselves, it must, as we have already suggested, be borne in mind that the development of the central nervous system *has not yet been completed at birth.* Such anomalies and deviations in its development are therefore in a given case not necessarily or entirely *ante*natal, though often commencing and perhaps already well established at a comparatively early period of intra-uterine life. In this connection it may be recalled that, in the terminology of human development, the "**embryo**" is regarded as becoming transformed into the "**fœtus**" during the seventh week (Arthur Keith [1]), and that, in its literal sense, the term "congenital" implies nothing more than something "innate," something "existing at and from birth." Many anomalies, although their inception dates from the period of embryonic or of fœtal life, may not only persist but continue to develop *after* birth; or the presence of some innate weakness may conduce to the further progress of lesions already in existence and perhaps already pronounced in degree. Again, some pre-existent "congenital inferiority" of tissues or organs may lead to the development *after* birth of what might otherwise have been regarded as a *de novo* post-natal disease.

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[1] "Porencephaly," from Greek, *πῶρος, pōros,* hard material, stone such as marble, hence metaphorically a hardened tissue, especially callus, and here localised hardening of brain-tissue.

[2] Syndrome, from the Greek *σύνδρομος, syndrŏmos,* a running-together, the meeting-place of several roads, hence metaphorically a concurrence or combination of symptoms.

We consider certain important examples of syndrome-diseases, **tuberous sclerosis** on p. 1134, and **multiple neuro-fibromatosis** on p. 1135, in which the disorders are characterised by the presence of multiple tumours of various kinds. **Other examples of such syndrome-diseases are :—**

(1) **HEPATO-CEREBRAL DEGENERATION,** or **Wilson's Disease,** so called because it was first described by Kinnier Wilson (1912) under the more restricted term **hepato-lenticular degeneration,** sometimes also called **progressive lenticular degeneration.** The syndrome typical of this disease affects especially adolescents and young adults and is characterised clinically by mental deterioration, the presence of brownish-yellow pigmentation of the cornea, and muscular symptoms—tremor and rigidity— due to involvement of the extrapyramidal neurones. As implied by the various names given to the disease, the "inborn weakness" affects more especially the **liver** (with the presence of a coarse atrophic **cirrhosis** of Laennec-type (p. 772), usually accompanied by splenic enlargement) and the **lentiform nucleus,** particularly the neostriatum or putamen, of each side—to which, however, it is now recognised that the degenerative changes are not confined, as they may, though in lesser degree, affect, for example, the caudate nucleus and cerebral cortex. The nerve-cells show various stages of the progressive degenerative process, from eccentricity of the nucleus up to disintegration and complete disappearance of the whole cell. These changes in the neurones are accompanied by glial proliferation, sometimes with the presence of "monster" glial cells like those seen in tuberous sclerosis (p. 1134); whilst, later, such proliferation is not infrequently followed by patchy softening and cavitation, which gives a spongy or worm-eaten appearance to the affected areas in the basal nuclei. Secondary or Wallerian degeneration in the extrapyramidal fibres belonging to the degenerated neurones of the neostriatum follows, thus accounting for the symptoms of muscular tremor and spasticity from loss of the controlling and co-ordinating influence of these cells over the lower neurones in the anterior or ventral horns of the spinal cord. An interesting point in connection with the heredo-familial incidence of this disease is that, not only are cases of the fully developed syndrome found in several members of one family, but the isolated occurrence of cirrhosis of the liver *without* involvement of the corpora striata has been detected in brothers or sisters of such patients, thus suggesting that Laennec's type of hepatic cirrhosis is itself due, at all events in part, to a congenital or heredo-familial predisposition, and is not necessarily brought about entirely by alcohol or other toxic substances, which may thus perhaps be regarded as acting as the exciting agents of its production in an organ already the site of "congenital inferiority" (B. Brouwer, of Amsterdam, 1916) (pp. 777–8).

(2) **HÆMOCHROMATOSIS.** The pigmentary changes in the various organs and tissues characteristic of this uncommon disease are described on pp. 227, 774, 793 and 804. The disorder itself is to be regarded as one of the group of diseases due to a familial "congenital inferiority" now under discussion and tends to affect the brain as well as the pancreas, liver, kidneys and suprarenals, bone-marrow and skin. In the brain, according

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[1] "Human Embryology and Morphology," 5th Edition, 1933, p. 64, by Sir Arthur Keith: During the seventh week, the embryo becomes a fœtus, by the end of which period the nasal, maxillary and mandibular processes (Fig. 389, p. 703) have united to form the face. "In the embryo the various parts of the adult body are only indicated; in the fœtus these parts have assumed their definite form" (3rd Edition, 1913, p. 40).

to Brouwer[1] (1936), changes analogous to those seen in Wilson's hepato-cerebral disease are liable to occur in the putamina, caudate nuclei and also in the cerebral cortex. The disease is found almost exclusively in males, and is believed to be an "endogenous disturbance of metabolism, especially of iron and protein, of unknown origin," and may be included in the same category as cases of congenital porphyrinuria and alkaptonuria (p. 227). The most important of the pigments,[2] the presence of which is characteristic of this disease, is the iron-containing **hæmosiderin,** which is here not derived from a more active destruction of the hæmoglobin of the red corpuscles—nor is the disease characterised by anæmia. The tissues are said to possess "an increased avidity for iron," and the diagnosis of the disease can be confirmed during life by obtaining the Prussian-blue reaction in sections of an excised portion of the pigmented skin or by spectroscopic analysis of it for iron. The symptoms associated with the involvement of the brain are muscular tremor and ataxia, and progressive mental deterioration.

(3) **THE LIPOIDOSES.** A group of allied diseases, the **lipoidoses,** have been described, in which it is claimed that there are inborn abnormalities of lipoid metabolism, with the accumulation of fatty material in the **nerve-cells** of the whole central nervous system, as well as in the **reticulo-endothelial cells** of the liver, spleen, bone-marrow and lymph-nodes —in which the changes have been described as a "generalised lipoid reticulo-endotheliosis" (*see* p. 1263). As far as the nervous system is concerned, it is sufficient to enumerate the three main types recognised, together with the nature of the lipoid in each.

(i) **The Hand-Schüller-Christian syndrome** or **diabetic exophthalmic dysostosis,** characterised, in typical cases, by defects in the bones (*e.g.*, of the skull and pelvis) in addition to the accumulation of **cholesterol** in the cells of the brain and cord, liver and spleen (pp. 202–3, 689 and 700). The tuber cinereum and hypothalamic nuclei are believed to be the site of the primary lesion. Various atypical and incomplete examples of the syndrome have been recorded.

(ii) **Gaucher's disease,** in which the **spleno-hepatomegaly** (pp. 689 and 700) is accompanied by the accumulation of the **kerasin** in the cells of the central nervous system. The disease, although it starts in childhood, runs a very slow and chronic course of perhaps fifteen or twenty years.

(iii) **Amaurotic[3] family idiocy, cerebro-macular degeneration** or **Tay-Sachs' disease,** in its infantile form, is a disease confined to the Hebrew race. It is a typically "heredo-familial" disorder, and is characterised by degenerative swelling of the nerve-cells throughout the entire nervous system including the retina, the progressive nature of changes in which leads to blindness, the macula showing through the overlying thinned and atrophied tissues as a cherry-red spot. The cell-bodies of the neurones become distended by an accumulation of lipoids of the nature of lecithin, phosphatide and lipochrome, and many of their dendritic processes also come to show irregular swellings. The nucleus becomes pushed to one side and the Nissl-granules are reduced in number and may disappear. The axons of many of these swollen cells undergo secondary degeneration, and myelin and neutral fat are demonstrable in the numerous foam-cells or phagocytic histiocytes with which the affected parts of the nervous tissues become crowded. These changes in the neurones are accompanied and followed by widespread glial proliferation.

The symptoms corresponding to these neuronal lesions include progressive mental deterioration ending in complete idiocy, blindness, paresis and paralysis. **Late infantile** and **juvenile forms** are described, the older children so affected being, however, not necessarily of Hebrew race, and the cerebellum especially being often involved and of small size from imperfect development.[4]

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[1] "The Spleen, the Liver, and the Brain," *Proc. Roy. Soc. Med.*, 1936, **29**, 579.

[2] The presence in hæmochromatosis of a pigment which they call "hæmofuscin," and which is said not to give a reaction for iron, has been described by some writers, though this is contradicted by others who state that failure to demonstrate iron in it is due to the inadequate methods employed. Its occurrence and nature have, however, been questioned, and several different pigments have been described under this name. An excess of melanin in some situations is also recorded by some authors.

[3] Greek ἀμαύρωσις, *amaurōsis,* a dimming (of the sight), hence blindness, partial or total.

[4] "Cerebromacular Degeneration," by E. D. Macnamara, W. E. Carnegie Dickson and T. R. Hill, *Jour. Neurol. and Psychopathol.*, 1933, **13**, 211.

Closely allied to the amaurotic family idiocy of Tay-Sachs' type and by some neuropathologists believed to be identical with it, is the **Niemann-Pick form of Hepatomegaly** (p. 700). Both anomalies appear occasionally to co-exist in some individual cases, and both also attack Hebrew infants, usually in the first year of life. Whether the **disturbance of lipoid metabolism** with its associated mesodermal **reticulo-endotheliosis** of liver, spleen, bone-marrow and lymph-nodes, is to be regarded as the primary lesion, or the **lipoidosis** of the ectodermal **nerve-cells,** is a question still requiring elucidation and involving problems of considerable importance in the study of general metabolism.

LESIONS OF THE CORPUS STRIATUM

Degenerative conditions affecting especially the **pallidum** and/or the **substantia nigra** tend to produce muscular hypertonicity and the **Parkinsonian syndrome,** so called because in 1817 it was first described by Dr. James Parkinson as occurring in **paralysis agitans.** It is characterised by tremor and muscular rigidity and, owing to the damping down of emotional, and the enfeeblement of voluntary, muscular movements, it gives rise to the frozen, mask-like and expressionless facies known by his name, and to the characteristic peculiarities of posture and gait. Paralysis agitans occurs in elderly persons, although juvenile cases have been recorded by R. Hunt (1917) and L. van Bogaert (1930). The analogous Parkinsonian syndrome produced by **epidemic encephalitis** is described on p. 110, and a similar or analogous condition is sometimes caused by syphilitic, and by arterio-sclerotic, and occasionally by traumatic, lesions of the pallidum, which may also be especially affected in poisoning with carbon monoxide (p. 1186) and manganese.

In contrast with these Parkinsonian symptoms, are the jerky and writhing, exaggerated and " purposive " movements and *hypo*tonicity of the muscles in **chorea** and **athetosis,** produced by lesions of the corpus striatum—particularly, it is said, in the putamen and caudate nucleus—and also, in some cases, in the optic thalamus. It has been pointed out that these choreic and athetotic movements are fragmentary and disordered forms of emotional and voluntary muscular actions, and are of the nature of an ataxia. **Sydenham's chorea** is a toxic or infective disease particularly of childhood and adolescence, and is usually associated with acute rheumatism (p. 452), but occurs occasionally during or after other infections such as scarlet fever, or as a complication of pregnancy (chorea gravidarum), in relation to all of which streptococci are of ætiological importance.

Huntington's chorea is a hereditary, chronic and slowly progressive disorder, commoner apparently in America than in this country. It affects the cerebral cortex, particularly of the frontal lobes, and the **caudate** and **lentiform nuclei,** especially the **putamen,** with profound degenerative and destructive changes in the nerve-cells and their replacement by proliferated glial tissue. Owing to the resulting atrophic shrinkage of the brain as a whole, some degree of dilatation of the ventricles and resulting internal hydrocephalus is common. The choreic symptoms and mental deterioration of this disease appear first as a rule in middle age, but commence occasionally in childhood.

Bilateral congenital athetosis or **choreo-athetosis** is one of a group of closely allied conditions of which it is the most characteristic from a pathological point of view (Fig. 655). It is associated with a curious light and dark mottled or marbled appearance of the **caudate nucleus** and the **striatum,** especially the **putamen,** as well as elsewhere (*e.g.*, in the **cerebral cortex**), to which the name "**status marmoratus**" (*état marbré*) has been given. As it has been found in the brains of still-born infants, it is definitely "congenital" in origin, unlike "unilateral athetosis" which can be produced, by, amongst other causes, birth-injury. Cecile and Oskar Vogt (1920 and 1925) describe the change as a lesion in the basal ganglia, with disturbance of myelination and patchy breaking-up of the affected ganglia, in which the destruction of the nerve-cells is accompanied and followed by glial proliferation.

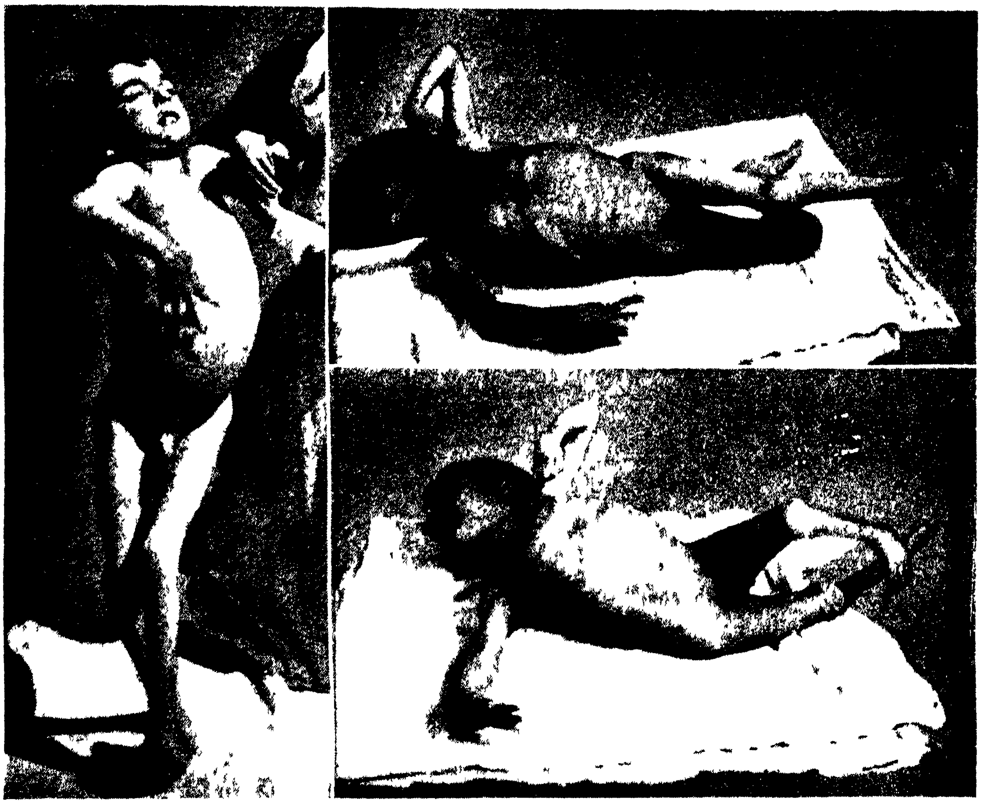

FIG. 655. *Bilateral congenital athetosis* or *choreo-athetosis* in a boy aged seven years, showing characteristic attitudes, club foot, etc. A "familial" case (one sibling a stillborn boy, another died aged seven months of "spastic paraplegia," seven and two years respectively before patient's birth). (Dr. T. Rowland Hill's case, W.E.H.)

THE HEREDITARY AND FAMILIAL ATAXIAS

The nomenclature of this group is still in a fluid state and each "clinical entity" or "syndrome" often has several synonyms; and various intermediate and allied forms are also found. Especially the **long ascending and descending tracts of the spinal cord** are affected, and, according as attention is fixed upon these or upon their origins and destinations—for example, **in the cerebellum** or in the **cord** itself—disorders of this group have been designated as "**cerebellar**" or as "**spinal**" or other denomination of **ataxia**. Some series of cases, e.g., of Friedreich's Disease, have been mainly **familial,** *i.e.*, amongst siblings (p. 1069); whilst in the ataxias associated with the names of Pierre Marie, Sanger-Brown and others, the disease is often definitely **hereditary,** and found in more than one, and sometimes in several, generations of an affected family. It is convenient, therefore, though in some individual instances perhaps not strictly accurate, to refer to the whole group as the "**heredo-familial ataxias,**" of which we need mention here only two of the more important sub-groups.

Friedreich's ataxia is described by some writers as a "familial" spinal ataxia, by others as a "hereditary" disorder, *i.e.*, there appear to be two factors, one dominant and the other recessive, in its causation. Isolated or sporadic cases also occasionally occur. Though appearing sometimes at or about puberty or later, the clinical manifestations are most frequently noticed first in childhood, slowness in learning to walk being not infrequently one of the earliest symptoms to attract attention; and, by the period of adolescence, the phenomena of the disease are usually well established. Inco-ordination of muscular movements, first of the lower limbs with ataxia and staggering gait, and later of the arms with intention-tremor, supervene, together with disordered speech from involvement of the muscles of articulation (dysarthria), nystagmus, abnormalities in the muscular reflexes and progressive paralysis and disuse-atrophy of the muscles. Characteristic deformities are practically always present, affecting the feet (pes cavus), hands (manus cava), and vertebral column (scoliosis).

The chief factors in the production of these phenomena are lesions in various tracts of the spinal cord. The most typical of these are the demyelination and dense glial sclerosis of the dorsal and lateral columns. The fasciculus gracilis of Goll (postero-internal tract) is affected throughout almost its entire length, and the postero-external fasciculus cuneatus of Burdach to a lesser extent. The anterior and posterior spino-cerebellar tracts and the lateral cortico-spinal (crossed pyramidal) tracts also suffer, with resulting spastic paralysis. The cord is narrower than normal and may even have a distinctly slender appearance, especially in the cervical region, and the pia is thickened. There is degeneration and atrophy of many of the nerve-cells in the grey matter of both ventral and dorsal horns: and of Clarke's column, lying near the grey commissure in the dorsal horns of the thoracic and upper lumbar region. Some degree of atrophy of the dorsal roots and of the corresponding peripheral nerves may occur, but is not a constant feature; nor do the nerve-cells of the dorsal-root ganglia appear to be affected as they are in tabes dorsalis. In a proportion of cases the cerebellum is smaller than normal, but as a rule without any pronounced histological alterations, although there may be a moderate degree of degenerative change in the Purkinje-cells, and also in the cells of the olivary and red nuclei. It is thought that the disease is due to an arrest in the development of the various systems of fibres in the spinal cord, but whether of the nature of non-development (agenesia) or defective development from impaired vitality (abiotrophy) is not yet known. The lesion in the nerve-fibres and loss or absence of their myelin-sheaths is followed by dense gliosis, usually diffuse, but sometimes showing curious whorls or "tourbillons" arranged mostly around the small blood-vessels.

In **Hereditary Cerebellar Ataxia,** *described by Pierre Marie*[1] *in 1893, the* **syndrome of muscular inco-ordination with spasticity and progressive paralysis** *of the affected muscles, frequently associated with optic atrophy, is due to* lesions in the cerebellar cortex, especially the Purkinje-cells : in the spino-cerebellar tracts connected with the dentate nuclei of the cerebellum and the olivary nuclei of the medulla : and in the cortico-spinal (cerebrospinal or pyramidal) tracts, loss of the controlling influence of which over the motor cells of the ventral horns leads to spasticity of the affected muscles. These lesions are the cause of the undue smallness of the cerebellum and slender appearance of the spinal cord described above under "Friedreich's Ataxia." The dorsal columns and dorsal nerve-roots are, however, *not* affected ; nor are the deformities of the feet and spine, so characteristic of Friedreich's ataxia, found in hereditary cerebellar ataxia. Both sexes are attacked equally and the onset is gradual and at a rather later age-period. The disease tends to be slowly progressive and terminates in widespread paralysis and dementia.

For an account of other allied and intermediate varieties of "primary" **spinal** and **cerebellar ataxias,** with or without spastic and atrophic changes in the muscles—according to the tracts and grey matter involved—described by various writers (hereditary spastic paraplegia, Sanger-Brown's hereditary ataxia, and the progressive cerebellar degenerations described by Gordon Holmes, Dejerine and Thomas, Lhermitte and Lejonne and others)—special text-books should be consulted. The "projection" or "representation" of the cerebellum upon certain areas of frontal, parietal and temporal **cerebral cortex,** and how lesions of these are associated with the ataxias, are described in the Year Book of Neurology, Psychiatry and Endocrinology for 1938, Chicago, pp. 28 29.

[1] It is inadvisable to call this "Marie's Disease," as some half-dozen different conditions have been so named : acromegaly (1886), hypertrophic pulmonary osteo-arthropathy (1890), spondylosis rhizomelica (or ankylosis of the vertebral joints) (1898), cleido-cranial dysostosis (1898), as well as diseases in which his name is linked with those of other writers, *e.g.*, peroneal muscular atrophy of Charcot-Marie-Tooth (1886), Marie-Robinson's syndrome (diabetes with the presence of levulose in the urine and various nervous symptoms), etc.

SECTION X

THE NERVOUS SYSTEM IN METABOLIC AND DEFICIENCY-DISEASES

In the general account of vitamin-deficiency diseases in Chapter IV, references are made to the connection between **beri-beri** and other forms of **polyneuritis** and vitamin-B_1 deficiency (pp. 444–5 and 1180); to **pellagra** and, more particularly, B_2-deficiency (p. 445): and, in Chapter XVIII on Diseases of the Blood, p. 647 *et seq.* and p. 653, to the association of **subacute combined sclerosis** (p. 1157) with the deficiency-anæmias.

PELLAGRA (p. 445), a condition of particular importance in war-time, is a vitamin-deficiency disease, due more especially to **lack of vitamin B_2** (containing, amongst other component parts, nicotinic acid, and sometimes called the "**P-P,**" or the "extrinsic **Pellagra-Preventing, Factor** " of the vitamin-B complex) or, as suggested by Hugh S. Stannus (1940), perhaps also to deficiency of **riboflavine.**[1] In some cases of pellagra and beri-beri (*see* pp. 1077–8), the clinical signs have persisted on the administration of B_1 and B_2 (including nicotinic acid), but have rapidly cleared up on the intravenous injection of a sufficient amount of B_6—" adermin " or " pyridoxin " (pp. 444–5).

Pellagra occurs in epidemics in prison-camps, prisons, asylums and similar institutions, or in regions where the food is deficient in this particular group of vitamins, and especially where maize or millet is the staple article of diet. In Great Britain it occurs only sporadically, though partial or subclinical forms of the disease are probably common, and its occurrence has been noted, for example, amongst those who adopt an inadequate diet for purposes of " slimming." In certain instances it may be due to **non-assimilation** of the vitamin even although present in the food, owing to gastritis or gastro-enteritis—*e.g.*. in bacillary dysentery. As might be expected from the nature of pellagra, attempts to convey it to animals by inoculation with the diseased tissues have been uniformly unsuccessful. Clinically, the disease occurs in **acute** and **subacute** to very **chronic** forms, lasting perhaps for many years. It is characterised by progressive weakness and cachexia : **cutaneous** manifestations such as erythema and symmetrical areas of dermatitis, especially on exposed parts such as the face, neck, wrists and hands, with liability of these to become pigmented : as well as by **digestive** symptoms, both as cause and effect, involving, in some cases, the whole alimentary canal from mouth to anus. In children, any persistent association of dermatitis and diarrhœa should suggest a possible diagnosis of some modified or partial form of pellagra. There is also progressive **mental** affliction, with symptoms pointing to lesions affecting the **nervous system** in any or all of its parts, but more particularly the **spinal cord,** its nerve-cells, especially those of Clarke's column, the motor nerve-cells of the ventral horns (as well as the corresponding cells of the cranial motor-nerve nuclei), the cells of the spinal dorsal-root ganglia, and the fibres passing from these into the cord and running up in the dorsal funiculi. Both pairs of spino-cerebellar tracts, anterior and posterior, may also be affected, and, because of involvement of the **cortical** motor cells, the corresponding nerve-fibres in the descending cortico-spinal (pyramidal) tracts. These lesions explain the various and varied nervous symptoms characteristic of the disease—tinglings, burning pains, numbness and anæsthesias, spastic or flaccid paresis or paralysis ; whilst involvement of the **basal ganglia,** especially the pallido-striatal : and the **extra-pyramidal system,** account for the tremor, choreiform and athetoid movements and the Parkinsonian facies (*cf.* p. 110) often present.

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[1] " Pellagra," by Hugh S. Stannus, *Lancet*, 1940, i, 352, a paper which should be consulted for details as to the chemistry of these substances, the " catalyses of the coenzyme-oxidase system in the oxidation of certain metabolites," and the possible disturbances in the various links in the chain of these processes in pellagra. Stannus also suggests that there may be a " synthesis of a pellagra-preventing factor in the stomach analogous to Castle's factor in pernicious anæmia," and he quotes instances of the successful treatment of pellagra with human gastric juice and with ventriculin and hydrochloric acid.

The lesions in the affected nerve-cells include especially chromatolysis or solution and disappearance of the Nissl-granules, and eccentricity and degenerative changes in the nuclei, with consequent degeneration of the corresponding nerve-fibres, which show swelling, thinning, and beading or fragmentation of the myelin-sheaths both in the nerve-tracts of the neuraxis and in the peripheral nerves. The changes in the axons themselves are usually less pronounced. Kinnier Wilson (1914) records a special increase in metachromatic granules (the π-granules of Reich) demonstrable with thionin or toluidin blue in the cells of the sheath of Schwann. Depending upon the degree of chronicity of the disease, varying grades of glial sclerosis ultimately supervene in the degenerated nerve-tracts of the neuraxis.

Other diseases in which vitamin-deficiency plays an important part are **lathyrism,** a demyelinating disease attacking the lateral, as well as the dorsal, columns of the cord, in persons whose diet has been restricted to food prepared from the *Lathyrus* or chick-pea : and the spasmodic or convulsive form of **ergotism** or chronic ergot-poisoning (see also under "Necrosis and Gangrene," pp. 244 *et seq.*), in which G. Barger (1931) and E. Mellanby (1931) have demonstrated that, in addition to the vascular phenomena produced by the consumption of contaminated rye-bread, the demyelinating lesions of the cord (*e.g.*, in the dorsal columns) and in peripheral nerves are in part due to **lack of vitamin A** in the diet.

BERI-BERI, the predominating manifestation of which is a **demyelinating multiple peripheral "neuritis,"** [1] is a deficiency-disease (p. 444) brought about by deprivation of especially **vitamin B_1**, the so-called "antineuritic factor," [1] also known as "aneurin," "thiamin," "ryzamin-B" or rice-polishings concentrate (and, as has been suggested by the work of Edward Mellanby (1931), perhaps associated also with a deficiency in **vitamin A** (p. 439), the experimental lack of which in the diet of young animals such as puppies produced a demyelinating neuritis, a condition *not* caused by reducing or cutting out vitamin B_1 alone). Walshe believes that the accompanying involvement of the myocardium and of the central nervous system is due to a breakdown in the carbohydrate-metabolism of heart-muscle cells and nerve-cells (see under "Polyneuritis," pp. 1180–1 and 1184).

Geographically, beri-beri is a world-wide disease, and tends to occur in epidemics under unsatisfactory hygienic, but particularly under inadequate dietetic, conditions of life, for example, not only in many parts of Asia, Africa and South America, but also in asylums, prisons and concentration camps in Europe and elsewhere, especially in times of war and famine. Similarly, in sporadic cases, the onset of the disease may, in inadequately nourished individuals, be precipitated by the increased strain of, say, some infective disease, a surgical operation (aided, perhaps, by low preparatory and post-operative dieting and the administration of large quantities of glucose), or of pregnancy. In connection with the last of these, the liability to a special form of beri-beri has been noted in the **breast-fed infants** of mothers themselves the victims of beri-beri, the disease supervening in the child because of the milk of the mother being correspondingly deficient in the special vitamins concerned. Although serious and severe cases of beri-beri are rare in Great Britain, it is probable that many instances of neuritis attributed to other, though perhaps definitely **predisposing,** causes such as **alcohol,** or associated with **glycosuria** and **diabetes,** and in **bacterio-toxic diseases,** and perhaps also in some cases of polyneuritis induced by certain **chemical poisons,** are in reality due, in part at all events, to mild degrees of deficiency of one or several members of the vitamin-B complex. This is a point of some significance when it is noted that these vitamins have important catalytic functions in certain of the processes of carbohydrate-metabolism, *e.g.*, the oxidising of the intermediate products (lactic and pyruvic acids) of the digestion of glucose (pp. 444 and 1180–1). In Mellanby's opinion, deficiency of vitamin A also plays an important part in the production of these disorders. It has been suggested that the reason why so-called **alcoholic polyneuritis** is less common in beer-consuming than in spirit-drinking communities is because of the presence of protective vitamins, even if only in small amounts, in malted liquors. In all of these varieties of **polyneuritis,** the administration of vitamin B_1 (together with other associated vitamins) has proved of both prophylactic and therapeutic value. There is at present no evidence to support the view that the disease is due to the production of some hypothetical toxin in the bowel or that there is an auto-intoxication from the absorption of altered metabolic products.

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[1] We use here the commonly employed term multiple "neur*itis*" or "polyneur*itis*" because it is convenient rather than strictly accurate, as the "inflammatory" nature of these deficiency-produced lesions is certainly open to question ; and, further, the lesion affects, not only the nerve-fibres, but also their "nerve-cells" or neurone-bodies. The term "neuronitis" would therefore, in this connection, be less inaccurate than "neuritis." Similarly, the propriety of the use of the term "anti*neuritic* factor" as a synonym for the B_1 element of the vitamin-B complex is also equally open to question. (In this connection, *see also* p. 1180.)

The mechanism of the causation of diseases associated with hypovitaminosis and avitaminosis in general is discussed in Chapter XV (p. 439), but it may be noted here that much controversy has taken place as to whether beri-beri is brought about by (1) **deficient intake** of vitamin B_1 (and vitamin A), because of their diminution in or absence from the diet, for example, when this consists almost exclusively of, say, polished or decorticated rice, maize, millet, or white wheaten flour; (2) **inadequate absorption** through failure to assimilate the vitamins, even when present in the food—owing to gastro-intestinal diseases such as dilatation of the stomach due to pyloric stenosis, etc.; (3) **inability** of the organism **to "phosphorylate"** the vitamin (Chapter XV, pp. 444–5); (4) **loss** of vitamin B_1 because of **its excessive excretion** by kidneys abnormally sensitive to it: or (5) any **combination** of these various factors. For a further note on the problem in relation to the carbohydrate-metabolism of nerve-cells and of the myocardium, *see* pp. 1180–1.

SECTION XI

CERTAIN DEGENERATIVE DISEASES OF THE BRAIN

of Undetermined Origin

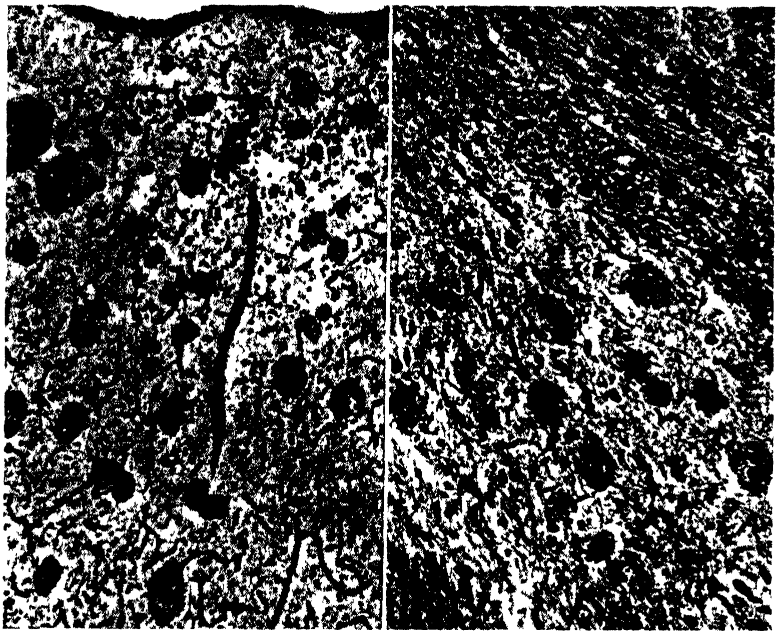
THE "ENCEPHALOPATHIES"

In some of the preceding sections of this chapter, an attempt has been made to enumerate various causes, obscure or otherwise, of lesions of the neuraxis. These causes may be congenital, hereditary, familial, traumatic and post-traumatic, toxic and infective; or they may be of the nature of defective or perverted nutritional factors, or associated with vascular, glandular, or other disorders and derangements. Amongst such causes must also be included the degenerative changes, normal or exaggerated, which supervene **in old age,** hastened, it may be, by association with any combination of the other factors mentioned. The actual histopathology of the nervous manifestations so produced is sometimes exceedingly complex, and may include any combination of co-existing destructive and reparative processes, both of them often progressive, the former affecting especially the neuronal, and the latter the glial supporting, tissues. Such changes are often insufficiently definite and specific to afford a satisfactory basis for the identification and classification of diseased conditions in individual cases, a difficulty only too familiar to every neuro-pathologist. Special anatomical sites may be attacked, or special tissue-elements picked out, and the investigation of a single case may occupy the time and resources of a team of several whole-time research workers, impossible in ordinary routine hospital work. Exaggerated normal involutional or senile changes can be studied in elderly patients suffering from, say, **senile dementia**—with the occurrence of peculiar lesions such as "senile plaques" and varying degrees of atrophy and sclerotic shrinking of the whole brain, and a complementary increase in the volume of the cerebrospinal fluid in the dilated ventricles or over the shrunken and retracted surface of the brain.

THE PRESENILE DEMENTIAS. These constitute a somewhat heterogeneous group of conditions which tend to supervene in late middle age, *i.e.*, during the period of involution, more especially in constitutionally predisposed persons. Many factors take part in the causation of premature senility, amongst which—along with deficiencies in ductless glands and vitamins—perhaps the most important are arteriosclerotic and other forms of vascular degeneration, cerebral syphilis, trauma, slow-growing neoplasms (for example of the corpus callosum and neighbourhood of the third ventricle), and certain toxic and infective conditions, including chronic alcoholism. In addition to these disorders, in or on which presenile dementia may supervene as a **secondary** phenomenon, there are two more important, and several rare, forms of the latter, which, though of unknown origin and therefore sometimes called "**primary,**" are at present regarded as specific "clinico-pathological entities." Because of their still unknown nature, they are meantime conveniently, if unscientifically, designated by the non-committal names of the authors who first described them.

(1) **Pick's disease** is a comparatively circumscribed progressive degeneration and atrophy affecting the cortical nerve-cells, chiefly and most frequently of the frontal, and next in order the parietal and temporal, and much less frequently the occipital, regions of the brain. Though occurring occasionally as early as the third decade of life, the disease supervenes most frequently between the ages of fifty and sixty, and especially in women. It may be acute or chronic, with a course of three or four or even as long as ten years. It is occasionally familial in incidence, and has apparently for its pathological basis the "primary" degeneration and disappearance of the nerve-cells, followed by a varying degree of gliosis with shrinking of the hemispheres and consequent dilatation of the ventricles.

(2) **Alzheimer's disease**, usually regarded as non-hereditary and non-familial (familial cases *do*, however, occur), is a progressive presenile degenerative process attacking all the layers of cortical nerve-cells, particularly of the frontal, but also of the occipital and other lobes, producing numerous minute scattered patches of necrobiosis. It is found also especially in the region of the hippocampal gyrus, but is sometimes more widely distributed throughout the brain and may be found, for example, in the basal ganglia and cerebellum. Patients, chiefly—though not exclusively—in middle and late-middle life, are affected, and the most characteristic feature of the lesions is the presence of rounded, ovoid, stellate or irregular "**senile plaques,**" perhaps 60 to 90μ in diameter, often associated with curious wisp- or skein-like "**tangles**" of the neurofibrils and axons of some of the affected nerve-cells in and around which or their remains these are loosely wound (Fig. 657, D and E). In the plaques there is proliferation, first of the micro-, and then of the macro-glial cells (Fig. 657, F), and an accumulation of silver-positive granular debris. The ganglion-cells, in addition to the presence of "Alzheimer's tangles" and along with the more usual degenerative phenomena seen in nerve-cells, show increased pigmentation, lipoid degeneration, vacuolation and shrinkage. Chronic sclerotic changes supervene, with shrinking and retraction of the affected regions of the brain, often widespread in the cerebral cortex, basal ganglia, brain-stem and cerebellum, with resulting complementary accumulation of increased amounts of cerebrospinal fluid over the shrunken surface of the brain and in the retracted and dilated ventricles. In the cerebellum, large spindle- and club-shaped swellings develop on the processes of the Purkinje-cells, a phenomenon, however, occurring also as an ordinary senile change (especially in cases of dementia), as well as in cerebro-macular and other degenerative diseases associated with amaurotic idiocy (p. 1071). These various lesions found in presenile dementia may be regarded as



(A) (B)

FIG. 656. *Alzheimer's presenile dementia.*[1] Low-power views of frozen sections of (A) the occipital cortex of a female aged sixty-two years : and (B) the deep part of the hippocampal cortex of a similar case in a male aged fifty-one, both showing numerous *argyrophil plaques, glial proliferation*, etc., described in the text. Bielchowsky's silver-impregnation method. × 100.

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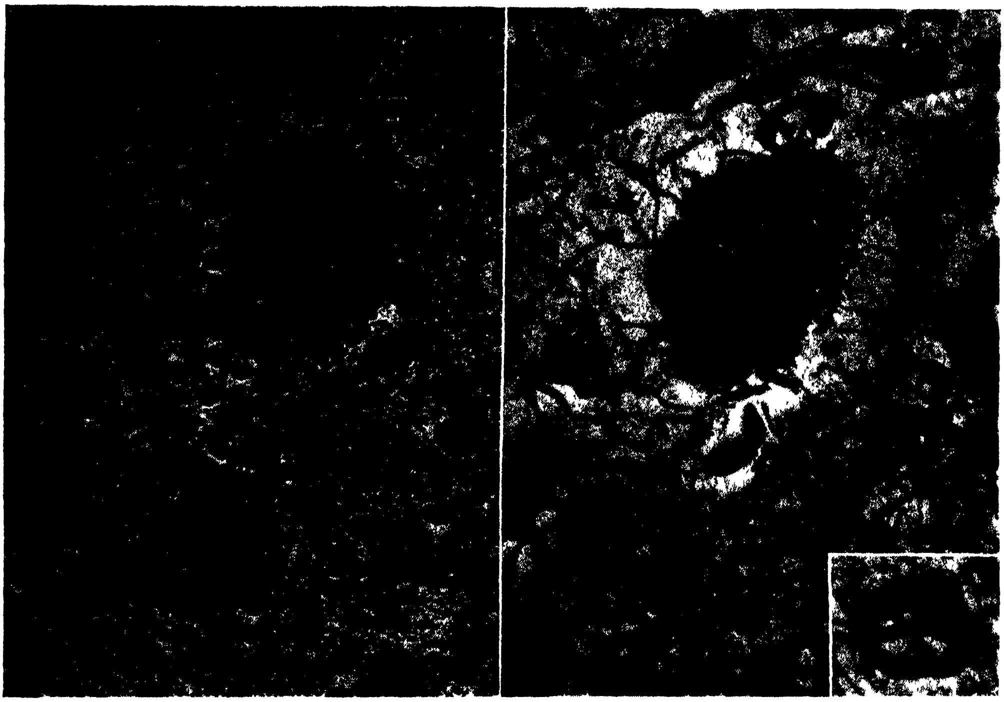
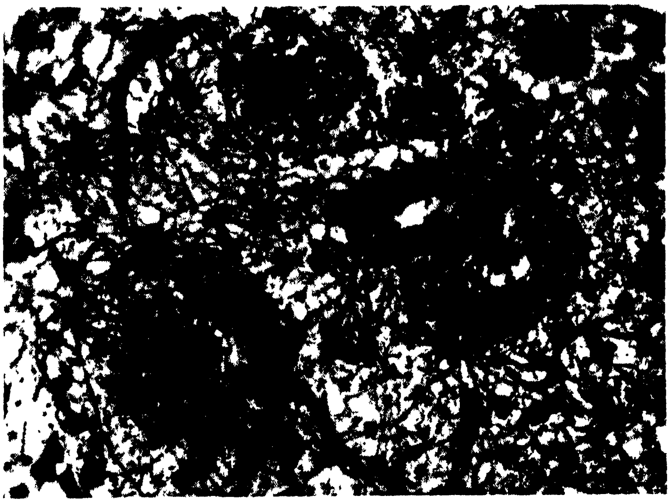
[1] These illustrations of presenile dementia are from West End Hospital and Shenley Hospital cases of Drs. C. Worster-Drought and W. H. McMenemey.



(C) (D) (E)

Fig. 657. *Alzheimer's presenile dementia.* High-power views of *argyrophil* " *plaques* " and *Alzheimer's* " *tangles* " ; (C) from same section as (A) in Fig. 656. (D) Section of hippocampal gyrus from a similar case, in which the " tangles " are numerous, and to which the description of them by Bouman (of Utrecht) is applicable : " knots, buds, eyes, a simple splitting-up of the neurofibrils, or a pathological increase of argyrophilia." (E) inset : a much coiled-up axon forming an Alzheimer's " tangle " round its cortical nerve-cell, from the same case as (B) in Fig. 656 opposite. Bielschowsky's silver-impregnation method. × 300.



(F)

Fig. 658. *Alzheimer's presenile dementia.* (F) High-power view of frozen section of frontal cortex from same case as (D) in Fig. 657, showing several *argyrophil plaques* : and *gliosis, with proliferation of astrocytes at the periphery of the plaques.* These figures are introduced here to illustrate in exaggerated degree some of the degenerative processes which supervene in old age, and at an earlier period in certain pathological conditions of the central nervous system. Bielschowsky's silver-impregnation method. × 300.

exaggerated and premature forms of the changes seen in old age—perhaps in predisposed persons—and in the production of which some toxi-infective or toxi-degenerative process or processes probably also participate.

(3) **Jakob's spastic pseudosclerosis** is a rare form of presenile dementia in which the degenerative processes are found, not only in the cerebral cortex, but also in the corpus striatum, especially in the putamen; and the liver may be cirrhotic, the syndrome thus linking up with that seen in Wilson's "hepato-lenticular degeneration" (p. 1070).

(4) Presenile dementia may also be associated with **Huntington's chorea,** a hereditary disease described on p. 1072.

SECTION XII

TUMOURS OF THE NERVOUS SYSTEM

The nervous system is one of the commonest and most important sites of neoplastic growth, both primary and secondary. As indicated on pp. 953–4, much study has been given to the embryogenetic derivation of its component tissues, and to the varieties of primary tumours derived from them; and many and varied classifications of these tumours have been proposed. In general terms, the nervous tissue is composed of the **ectoderm-derived** neurones or nerve-cell elements proper, with their axons and other processes: and the similarly-derived glial supporting tissues; whilst the meninges: nerve-sheaths (in whole, or possibly, accordingly to some writers, mostly but not exclusively): and the blood-vessels and their supporting connective tissue: are **mesodermal.**

For our present purpose, neoplasms derived from the tissues of the nervous system may be grouped and described under the following main headings:—

1. **Tumours of the Meninges, Cerebral** and **Spinal,** pp. 1083 to 1097.
2. **Tumours of the Neuraxis** (*i.e.*, the Brain and Cord), both **Neuronal** and **Glial,** pp. 1097 to 1128.
3. **Tumours of Peripheral Nerves** and **Nerve-Ganglia,** pp. 1139 and 1198.
4. **Vascular** and **Connective-Tissue Tumours,** p. 1093 *et passim* and pp. 1129–34.

Certain other tumours of importance in connection with the nervous system are discussed under the headings:—

Pineal Body or **Epiphysis Cerebri,** pp. 848 and 1120–22.
Pituitary Gland or **Hypophysis Cerebri,** p. 806 *et seq.*
Congenital and other **Tumours** and **Cysts** of, or in the neighbourhood of, these two organs, including:—
  Rathke's Intraglandular-Cleft Tumours and **Cysts**: and the so-called:—
  Craniopharyngiomas, derived from the walls of the pouch of Rathke (from which the glandular part of the pituitary is developed) or from " rests " of stomodœal squamous epithelium carried in with it, p. 818.

Some **melanomas** are amongst the most malignant tumours known (pp. 323–4). They arise occasionally from the melanoblasts and melanophores of the leptomeninges (p. 1095). From malignant pigmented tumours of the skin and eye, secondary growths are found in the brain in large numbers.

We are opposed to the classification of local granulomatous nodules as " tumours " (although the terms " tuberculoma," " syphiloma " or gumma, and even " actinomycoma," are now in current use). Clinically, for purposes both of diagnosis and of treatment, these granulomatous lesions *have to be differentiated from neoplasms or true tumours,* as have also aneurysms (pp. 493 and 1042-6) and certain other vascular abnormalities (pp. 496–7).

TUMOURS OF THE MENINGES

Considerable differences of opinion still exist as to the mode of origin of some of the primary tumours arising from or growing in connection with the cerebral and spinal meninges, particularly as to whether the leptomeninges themselves, and consequently the tumours derived from them, are of neuro-ectodermal or of mesodermal origin. Harvey Cushing's suggestion that such tumours, or at all events the more characteristic types of them, should be designated " **meningiomas** " is convenient, and does not postulate any particular hypothesis as to their exact embryological origin.

The following nine varieties of tumour are described by Bailey and Bucy [1] as originating from the meninges :—

(1) **Mesenchymatous tumours** containing mucinoid or myxomatous fusiform or stellate branching cells of primitive type resembling those seen in myxomas (p. 301).

(2) **Angioblastic type,** in which the tumour-cells themselves act as angioblasts and give rise to blood-vessels or blood-spaces, usually thin-walled and primitive in structure.

FIG. 659. *Meningioma :* an intracranial tumour removed from a man aged thirty-nine. Low-power view of a field adjacent to that illustrated in Fig. 660 showing a wide area of recent hæmorrhage and the early formation of large sinus-like vascular spaces, as well as the presence of numerous phagocytic "foam-cells" just commencing to simulate so-called "pseudo-xanthomatous" tissue. The darkly-stained structures are included collagenous fibrils. For the original structure of this tumour, *see* Fig. 669 on p. 1090. (W.E.H. case.) Hæmatoxylin and van Gieson. × 100.

Such proliferating neoplastic vessels are also frequently found in other varieties of meningiomatous tumour, especially where these have undergone secondary hæmorrhagic or necrotic changes,[2] the tumour-cells often tending to vascularise such areas by a process analogous to that occurring in the formation of granulation-tissue in a thrombus or exudate (p. 49 *et seq.*). These newly-formed vascular channels are at first merely lake-like open spaces in the tissue, lined by tumour-cells which may then flatten to form an endothelial lining. The spaces thus formed are sometimes intercommunicating and of considerable size, leading to the production of cavernous hæmangiomatous or less commonly lymphangioma-like tumours.

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[1] "The Origin and Nature of Meningeal Tumours," by Percival Bailey and Paul C. Bucy, *American Journal of Cancer*, 1931, **15**, 15, and pp. 43 *et seq.*

[2] "Certain Intracranial Tumours: Their Variability and Multiplicity," by W. E. Carnegie Dickson, *British Medical Journal*, 1933, **ii**, 1016.

The presence of primary angioblastic meningiomatous tumours is occasionally associated with angiomatosis of the retina and the presence in the cerebellum of an angioblastomatous cyst characteristic of the tumour-complex known as "Lindau's disease" (p. 1131).

(3) **Meningotheliomatous type** (or one form of "**Meningioma**" proper), tending to reproduce the structure of the arachnoid villi. As pointed out by Cushing, these tumours arise especially in localities where the arachnoid villi are themselves most usually situated, *e.g.*, in the central or fronto-parietal parasagittal region or on the falx cerebri : over the cribriform plate of the ethmoid (Fig. 661, p. 1086) : or in the lateral portions of the middle fossa of the base of the skull : and over the bones in the neighbourhood of the pituitary fossa and around the exits of the cranial nerves, etc. (Fig. 661) ; but meningiomatous tumours may be found elsewhere in connection with the membranes at the base of the brain, *e.g.*, in the neighbourhood of the foramen magnum, as well as in the spinal meninges. The arachnoid villi normally project into and through the dura (Fig. 569, p. 951), and small heterotopic collections of such arachnoid cells embedded in the substance of the dura are of frequent

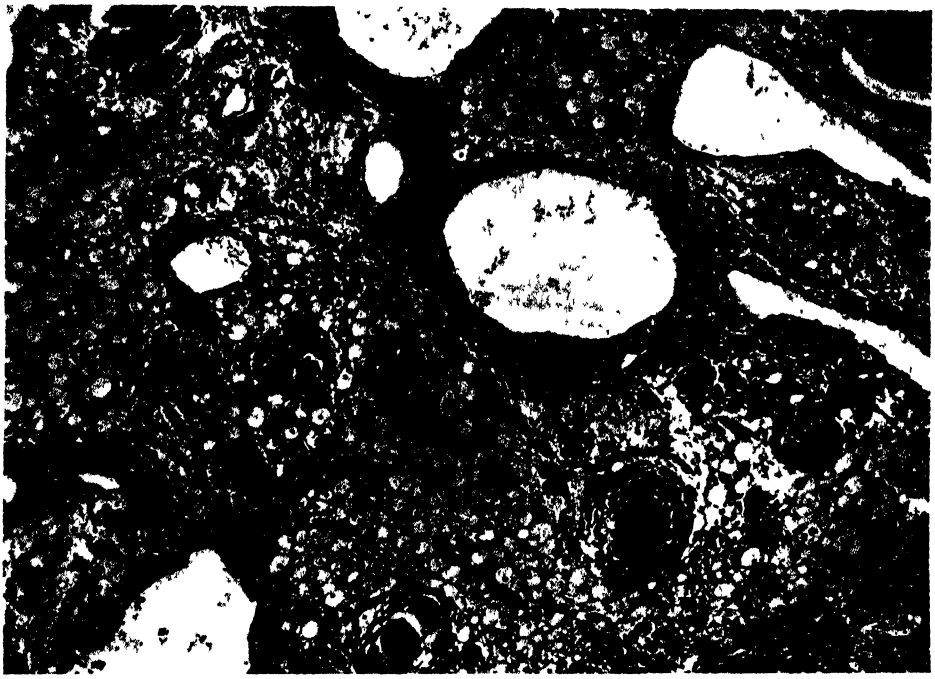

FIG. 660. *Meningioma* : from the same specimen as Fig. 659. Low-power view showing how such tumours, especially if the site of hæmorrhage or necrosis, may develop characters suggestive of "*angiomatous*," and of so-called "*pseudo-xanthomatous*,"[1] tumours. A few small concentrically-arranged psammomatous particles, some of them becoming calcified, still persist and indicate the original nature of the tumour, which is illustrated in Fig. 669, p. 1090. (W.E.H. case.) Hæmatoxylin and van Gieson. × 100.

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[1] In connection with "*xanthomatous*" and "*pseudo-xanthomatous*" reactions and lesions, *see* note on "Reticuloses and Reticulo-Endothelioses" and "Reticulo-Sarcomata" on pp. 1262–4 of our Appendix at end of book.

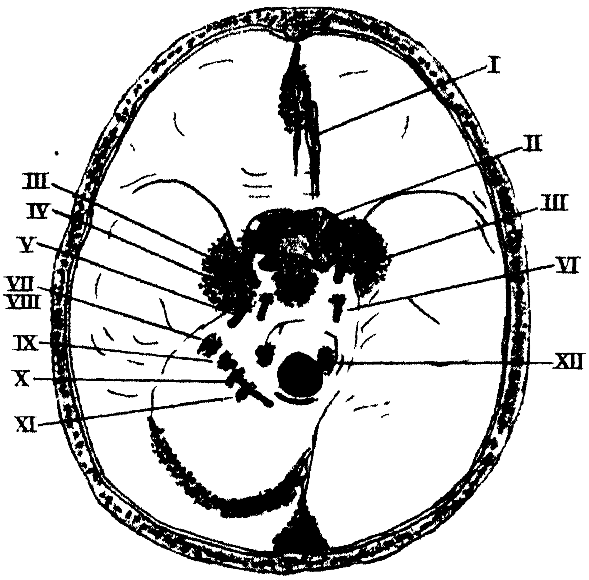


FIG. 661. *Sites of arachnoidal clusters* at base of skull, from which (as well as from the parasagittal and other groups) *meningiomatous tumours* originate. The numbers indicate points of entrance or exit of the cranial nerves. (From Harvey Cushing, after Aoyagi and Kyuno.)

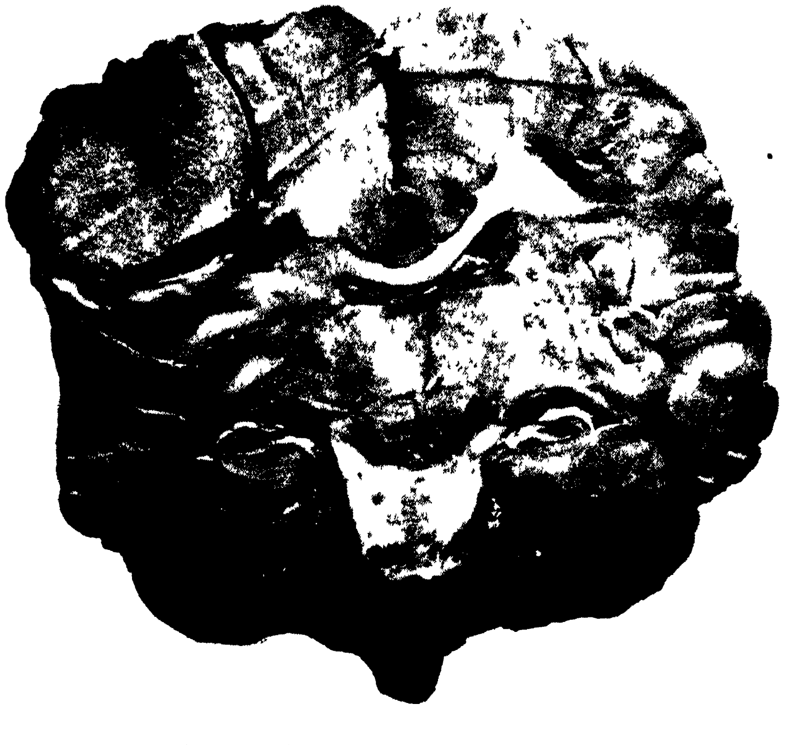


FIG. 662. *Meningioma*, deeply indenting, but not adherent to, and easily "shelled out" from, the right cerebral hemisphere of a woman aged fifty-two years (the surface hæmorrhage is operative). Note the distortion of the ventricles. (Dr. Yealland's case, W.E.H.)

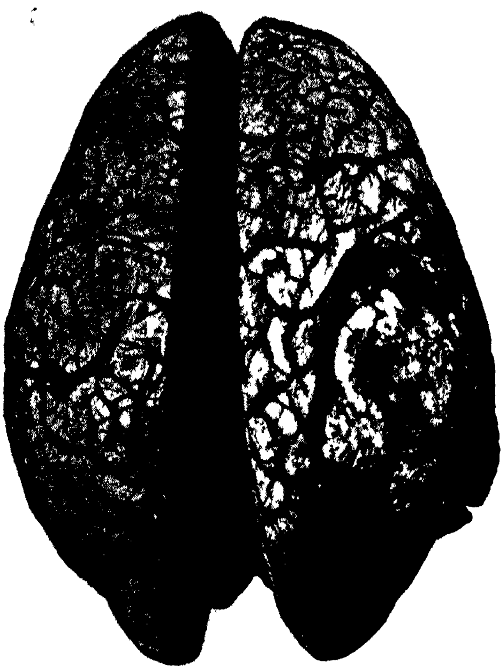


FIG. 663. *Meningioma* large tumour over right parieto-occipital region in a man aged forty nine years This specimen illustrates how easily some of these tumours "shell out" from the subjacent brain. (Dr. Macnamara's case, W E H)

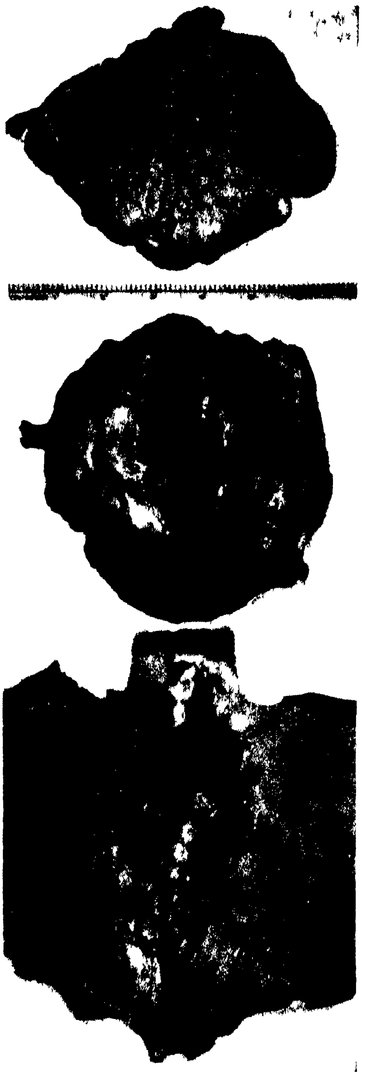


FIG. 665 *Meningothelioma* excised from a female aged fifty nine years. The middle figure shows upper surface of tumour covered by adherent dura The upper photograph is of the cut surface, and below is shown the frontal bone, from the roughened and eroded inner aspect of which the tumour had been separated (W E H case.) Two-thirds natural size.

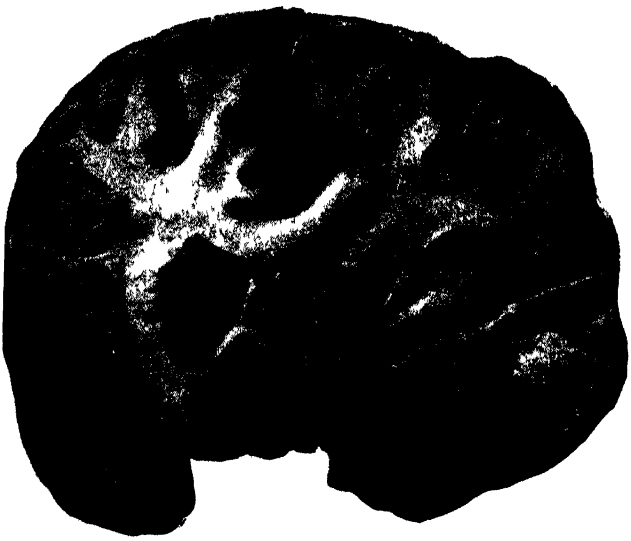


FIG. 664. *Meningioma:* coronal section of brain of male aged twenty.seven years, with tumour indenting left temporal lobe and showing the result of deep X-ray treatment (see Fig 666, p. 1088) Note the characteristic distortion of the ventricles produced by a tumour in this situation. (Dr. T. Rowland Hill's case, W.E.H.)

occurrence. It is, therefore, not surprising that tumours originating from these or from analogous arachnoidal structures are intimately associated with and firmly adherent to the dura mater, and were for long regarded as tumours of that membrane itself.

Though usually comparatively simple and generally regarded as "benign," they frequently **tend to penetrate and infiltrate the neighbouring bone,** but metastases are practically unknown. If situated beneath some part of the cranial vault, an appreciable and sometimes considerable localised thickening and bossing of the bone may indicate the site of a subjacent tumour. Erosion of the inner aspect of the overlying bone may also occur (Fig. 665). The tumour-mass is, as a rule, easily separable from the subjacent surface of the brain, but in some instances may be embedded in the brain and show little or no apparent connection with or adhesions to the overlying dura.

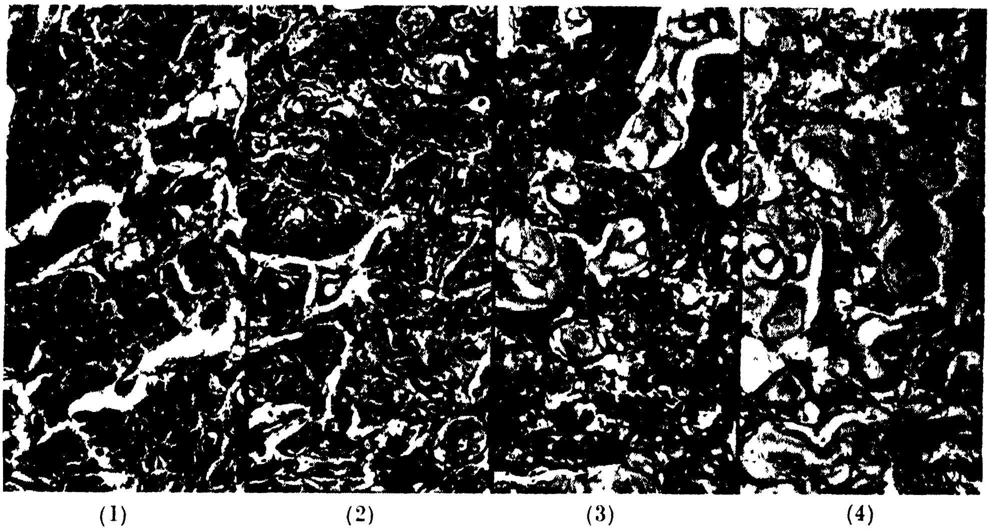


FIG. 666. *Meningioma* (*see* Fig. 664) after prolonged " deep X-ray " treatment showing progressive degenerative fibrotic and hyaline changes produced in cells and stroma. No. 1, van Gieson's method.
Nos. 2, 3 and 4, Mallory's stain for connective tissue. × 75.

In the meningotheliomatous variety of meningioma, a certain proportion of the tumour-cells may be plasmodial, with grouping of their nuclei and imperfect separation of the cytoplasm—a phenomenon sometimes exaggerated by deep X-ray treatment (p. 293), which may also produce fibrotic and degenerative changes (Fig. 666). The characteristic tumour-cells are spindle-shaped and tend to form interlacing bundles, and, though they do so more imperfectly than in the next variety (the psammomas), they may reproduce in varying degree the concentric whorled structure of the arachnoidal villi. Occasionally in multiple neurofibromatosis (von Recklinghausen's disease, p. 1135), **multiple meningiomas are** found projecting from the deep surface of the dura, these being, however, all primary in nature (*cf. below*, under Psammomas and Fig. 672, p. 1092).

(4) **Psammomatous type.** This is the most characteristic form of meningioma, and differs from the meningotheliomatous type in its more pronounced tendency **to whorl-formation,** especially round the small blood-vessels. The centres of

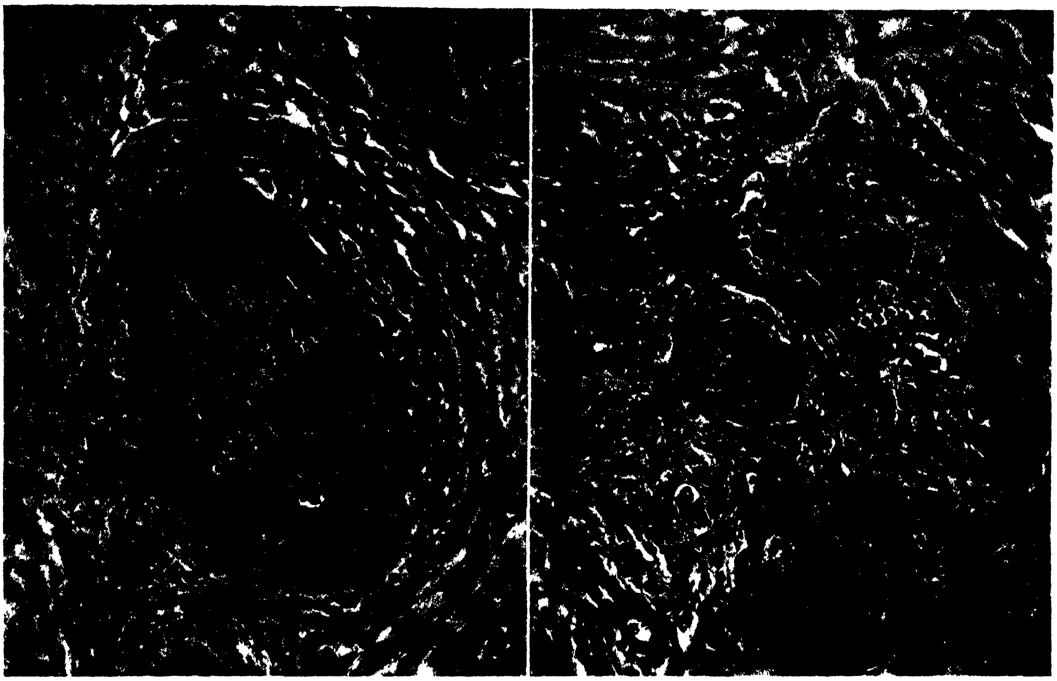


FIG. 667. *Meningioma* showing transition between the *meningotheliomatous* and the *psammomatous types*, the former more highly cellular and the cells more diffusely arranged or only in broad bands: the latter less cellular and arranged in whorls around small blood-vessels. From a female aged thirty-six years, in whom the diagnosis of " meningioma " was made during the operation by the findings shown in Fig. 668 below. van Gieson and hæmatoxylin. × 300. (W.E.H. case.)

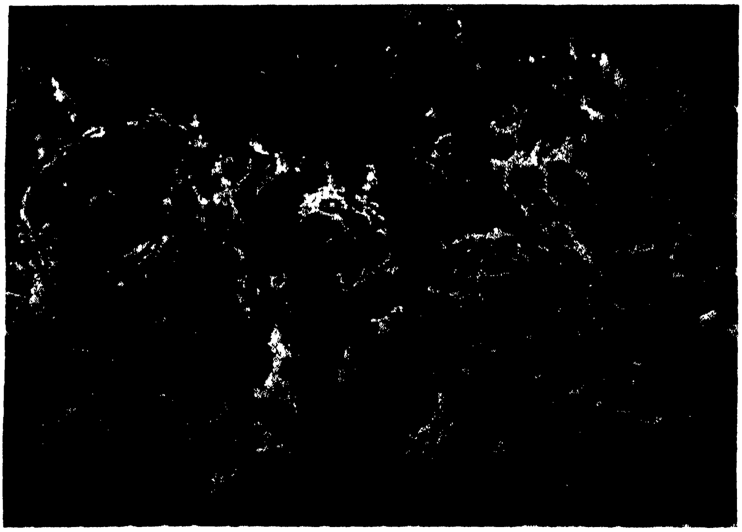


FIG. 668. *Meningioma* excised from neighbourhood of pituitary fossa in a female aged thirty-six years. From X-ray examination it was thought to be a suprasellar cyst; but, from this *fresh-wet preparation*, teased in toluidin blue, the tumour was diagnosed during the operation as a " whorled " or " psammomatous meningioma " (*cf.* Fig. 667 above). × 400. (W.E.H. case.)

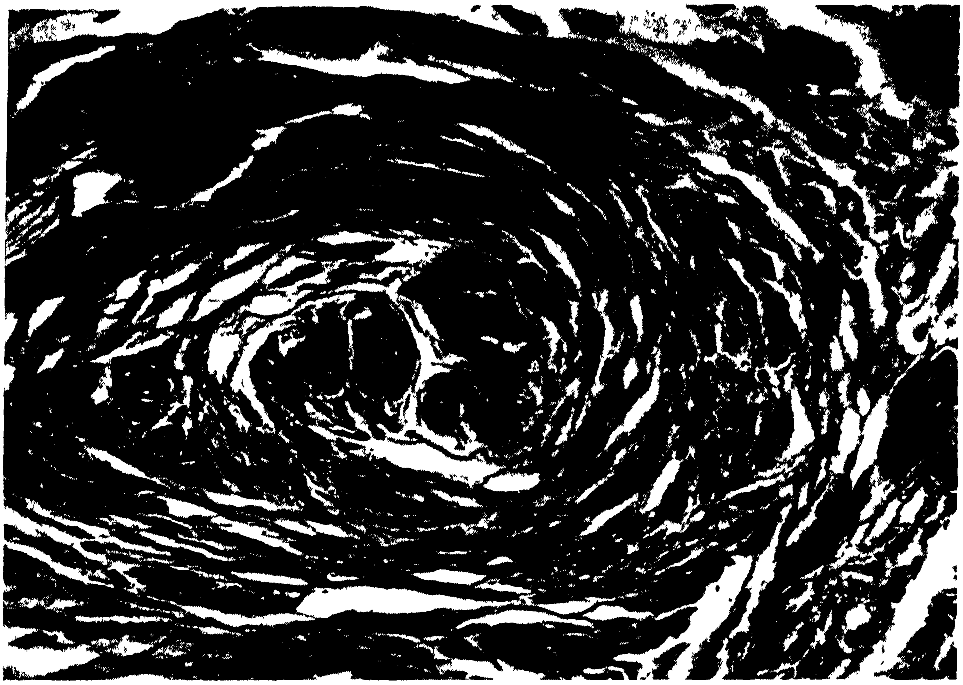
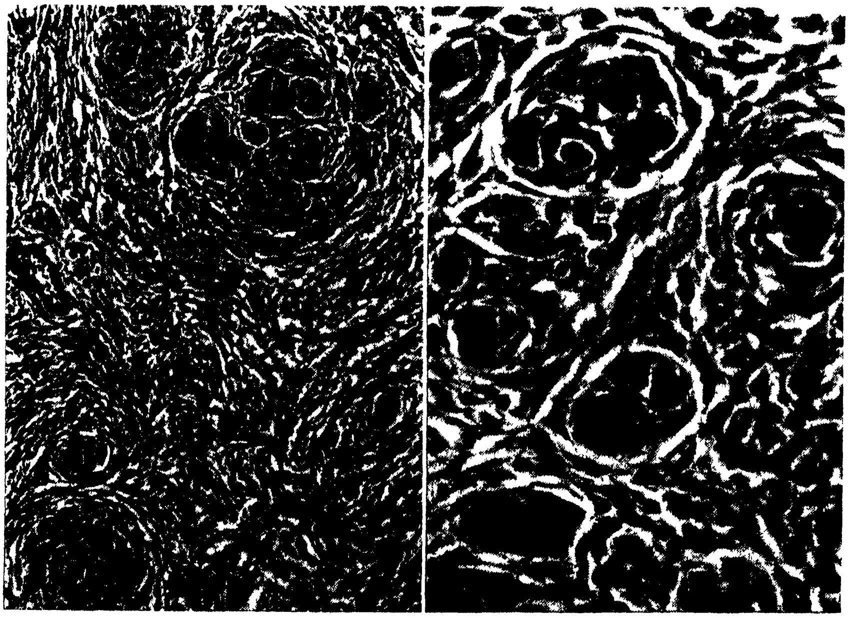


FIG. 669. *Meningioma.* High-power of another area of the same tumour as illustrated in Figs. 659 and 660, showing the whorled arrangement of the meningiomatous cells, *i.e.*, becoming "psammomatous" in type. (W.E.H. case.) Hæmatoxylin and eosin. × 400.



(A) × 100. (B) × 300.

FIG. 670. *Meningioma* removed by Mr. Geoffrey Knight from the left parietal region near the vertex, of a female aged forty-six years, showing transition from "meningotheliomatous" to "psammomatous" type. It was about the size of a hen's egg, and was adherent to the sagittal sinus and falx. (W.E.H. case.) Hæmatoxylin and eosin.

the whorls often undergo hyaline degeneration and later become calcified, with formation of the characteristic **corpora arenacea** or **brain-sand particles,** from which the term "psammoma"[1] is derived. **All intermediate stages** between the more purely cellular meningothelioma and the more chronic and slow-growing whorled and calcified psammoma are found (Figs. 667 to 671).

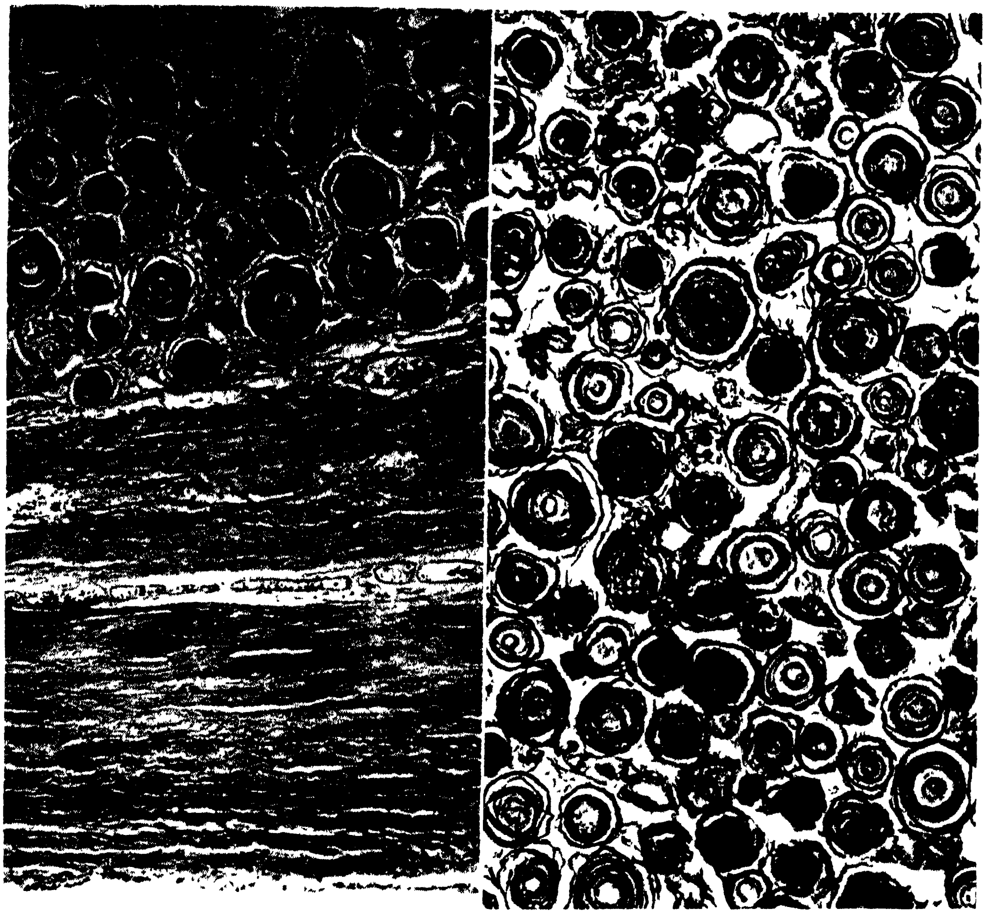


FIG. 671. *Spinal psammomatous meningioma.* Biopsy-specimen from a female aged fifty-five years. (A) Low-power view of section from the same case as Figs. 673 and 674, showing the attachment of the meningioma to the inner surface of the dura, which is itself comparatively non-cellular, but shows some thin-walled blood-vessels near the tumour. The concentric structure of the small psammomatous spherules is well shown. Many of the particles show a minute central blood-vessel with lumen still persisting; but, in other, and especially older, particles, this vessel is obliterated or has disappeared; (B) demonstrates the concentric structure round the small central vessels, which, in the more degenerated and calcified spherules, have become obliterated. (W.E.H. case.)
(A) Mallory's connective-tissue stain } × 100.
(B) Perdrau's silver-impregnation method } × 100.

The common sites of psammomas are identical with those of meningotheliomas (Figs. 661 and 662 to 665). They are most frequently single and sometimes of considerable size ; or, as noted above in the case of meningotheliomas

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[1] Greek ψάμμος, *psammos,* sand.

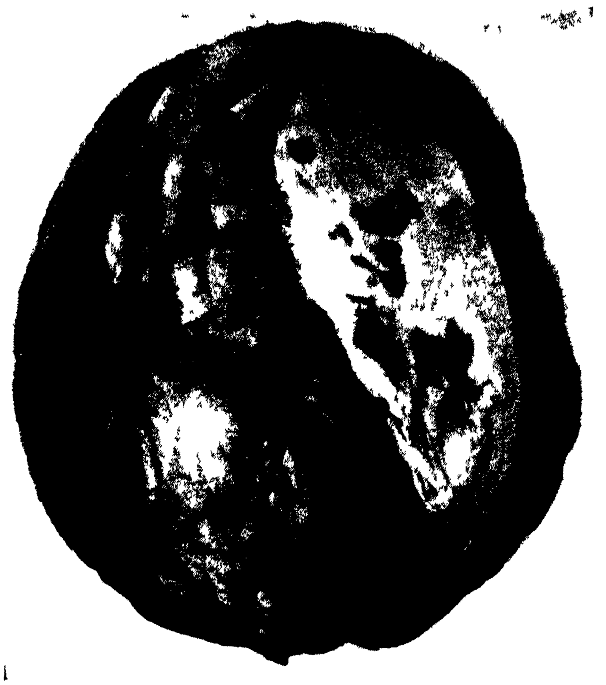

Fig 672. *Multiple small meningiomata* projecting from everted inner surface of the meninges (Wishart's syndrome) in a case of multiple neurofibromatosis (p 1135) in a male aged twenty-five years [1] (W E H case)

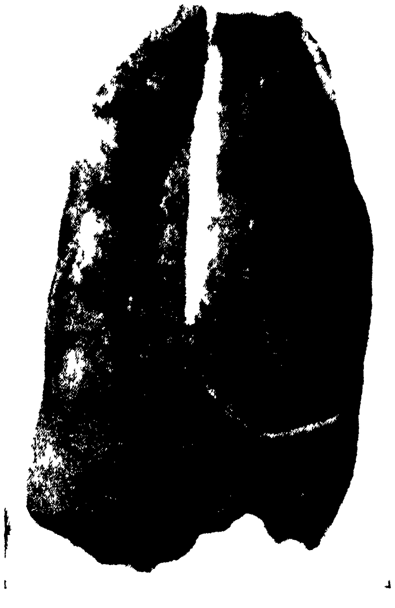

Fig. 673. *Psammomatous meningioma* attached to spinal meninges in lower thoracic region, from a female aged fifty-five years. The tumour is laid open to show the semi-translucent gritty and crumbling appearance, like wet sand (pale brownish-yellow in original specimen). For appearances in sections and in teased preparations of this tumour, *see* Figs. 671 and 674. (W.E.H. case.) Twice natural size.

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[1] Described in " Multiple Meningeal and Perineural Tumours with analogous changes in the Glia and Ependyma," by Worster-Drought, Carnegie Dickson and McMenemey, *Brain*, 1937, **60**, 85.

(p. 1088), they are more rarely multiple (" Wishart's syndrome," Fig. 672) and then usually smaller, as when they occur as part of certain " multiple-tumour complexes " or " syndromes," such as von Recklinghausen's disease (p. 1135).

In teased fresh-wet preparations of biopsy material, an immediate diagnosis can often be made by finding the psammomatous bodies (Fig. 668), which are sometimes attached to the blood-vessels like fruit upon the branch of a tree (Fig. 674).

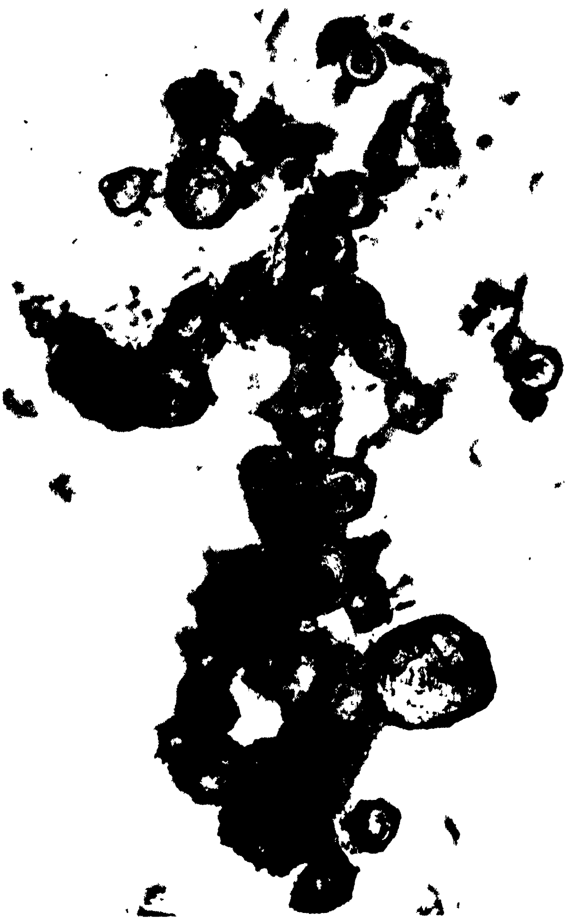


FIG. 674. *Psammomatous meningioma of spinal cord.* Low-power teased preparation of fresh biopsy-specimen from a female aged fifty-five years, showing the concentric structure of the spherical psammomatous particles, many of them completely calcified. They are arranged like fruit on a " stalk " of branching blood-vessels and connective tissue. Fig. 671 is from a paraffin-section of the same tumour (Fig. 673). Hæmatoxylin and eosin. × 100.

(5) **Osteoblastic type.** Varying degrees from mere calcareous plaques up to plates of fully-formed bone may be found in connection with the cerebral and spinal membranes, both dura and arachnoid. Calcified plaques are common and often multiple, especially in the leptomeninges of the cord (Fig. 751, p. 1165). Similar calcareous plates are common in the falx ; and fully-formed bony masses of varying size, usually comparatively small, are of not infrequent occurrence and originate by membranous ossification.

(6) **Fibroblastic tumours** of the meninges such as the ordinary fibroma (pp. 298–301) are uncommon and occur usually in the dura or one of its processes (Fig. 675, p. 1094).

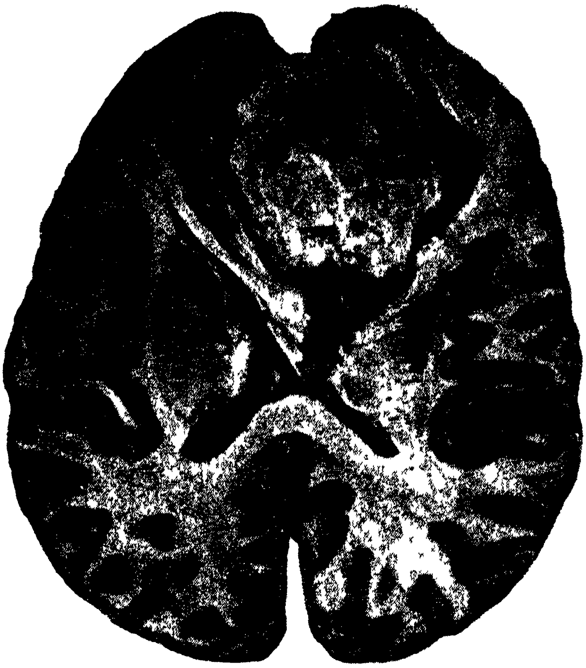
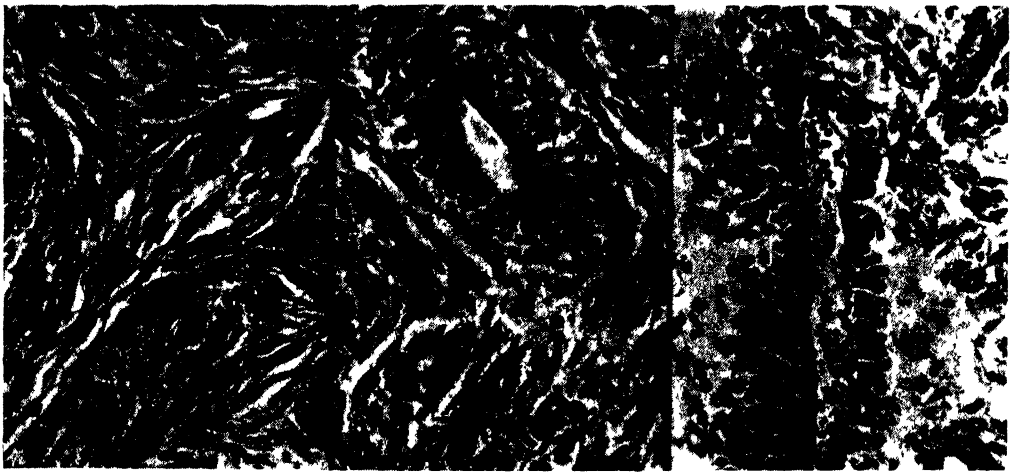


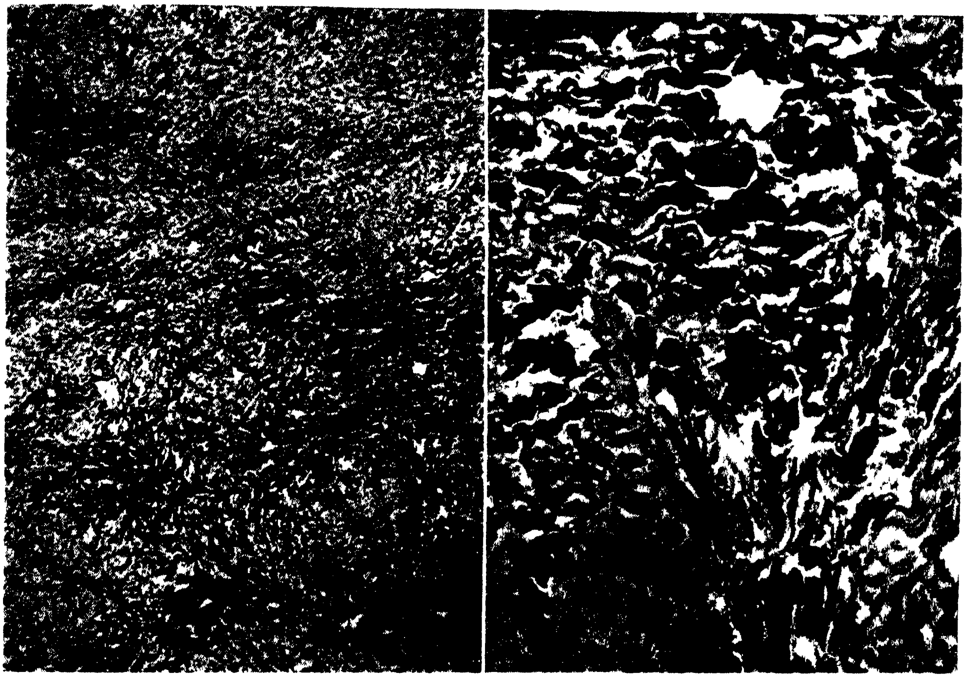
Fig 675 *Fibro meningioma* Horizontal section through the hemispheres of a man aged fifty one years, showing the variegated cut surface of the hard fibromatous tumour Note the moderate hydrocephalic dilatation of the lateral ventricles and the thin cyst like dilatation of the "fifth' ventricle behind the tumour (Dr Worster Drought's case, W E H)



(C) × 200 (D) × 200 (E) × 200.

Fig 676. *A "meningioma" or tumour of the spinal meninges*, showing, on tracing it inwards towards the spinal cord (*i e* , *upwards* in each of the photographs), gradual transition through the "phases" shown in Fig 677 (A) and (B) opposite histologically a "*melanoma*" or "*melanoblastoma*" The cells then form progressively less and less pigment and in (C) only an occasional tumour cell is pigmented, the cells as a whole now taking on a "*meningotheliomatous*" *type* and, in (D) and (E) becoming "*peritheliomatous*" around an '*angioblastic*" core, and, on the inner surface of the theca, forming a fine velvet-like pile of '*pseudo-papillomatous*" *processes.* These photographs are introduced here to illustrate *the histological variability of a single tumour* in its different parts. Hæmatoxylin and van Gieson's method.

(7) **Melanoblastic type.** A slight amount of pigmentation of the leptomeninges is more or less normal in certain areas, *e.g.*, over the medulla and spinal cord, and patches of pigment may also occur in the dura. In rare instances a **primary melanotic tumour** arises from the pigment-containing cells of the meninges. In connection with the nervous system, however, a commoner site of origin of primary melanoma is the **retina** (pp. 323–4) For Masson's view that many if not all **pigmented moles** of the skin arise in connection with the **end-organs of peripheral sensory nerves,** *see* p. 324. The distribution of the melanin-pigment in these meningeal as in other varieties of melanoma occurring elsewhere may be patchy and irregular; and in some instances the cells of certain similar but unpigmented tumours may, by special staining or impregnation-methods, be proved to contain the melanogens or uncoloured precursors of melanin (p. 323).



(A) × 75. (B) × 300.

FIG. 677. *Melanoma of spinal meninges,* compressing the fifth cervical segment in a man aged twenty-three years, producing "Froin's syndrome" in the cerebrospinal fluid (p. 963), and paresis of all four limbs the symptoms disappearing after excision of the tumour.

(A) Low-power view showing the growth arising apparently from a pigmented patch in the dura. (Several such patches were present in the immediate neighbourhood. For the nature and origin of "melanoblasts," *see* pp. 219 and 323.) The proximal tumour-cells are packed with pigment, but, further from the origin of the tumour, the pigment is present only in patches, and, farther still, merely in widely-scattered single cells. (B) High-power view of a portion of the same section, towards the right lower corner of (A), showing the spindle-shaped cells crowded with melanin-granules. In Fig. 676, on opposite page, further "stages" or "phases" in the growth of this tumour, seen on tracing it inwards through the membranes, towards the spinal cord, are illustrated. (By courtesy of Mr. F. W. Willway, Bristol.) van Gieson and hæmatoxylin.

(8) **Sarcomatous type. Fibrosarcomas** and **sarcomas** of the usual general types (p. 316 *et seq.*) arise from the fibrous tissue of the dura. From the leptomeninges, a variety of tumour closely resembling the melanoblastic type histologically, but **unpigmented,** may occasionally develop, especially in connection with the subarachnoid space in which it may grow and spread widely. These have been described under various terms, such as "sarcomatosis" or "endotheliomatosis" of the meninges, and when developing from the lepto-

meningeal sheaths of the blood-vessels of the brain may be described as **peritheliomatous** (Percival Bailey [1]). The peripheral or deepest part of the meningeal melanoma illustrated in Figs. 677 and 676 might be regarded as of this nature.

(9) **Lipomatous type.** In the human meninges these are rare, as are also the fat-cells from which they are derived. Lipomas were described by Virchow; and Bailey [2] has collected some 60 cases from the literature. They occur on the upper surface of the corpus callosum, less frequently about the tuber cinereum or corpora quadrigemina, and are usually regarded as being "congenital" in nature. Extradural lipomas may occur in the vertebral canal and compress the cord and its meninges from without (p. 1067); but such tumours are very rare within the spinal theca itself. (On a Plate illustrating "Meningeal Tumors of Lipoblastic Type," Bailey and Bucy include a "Xanthoma" with vacuolated cells.)

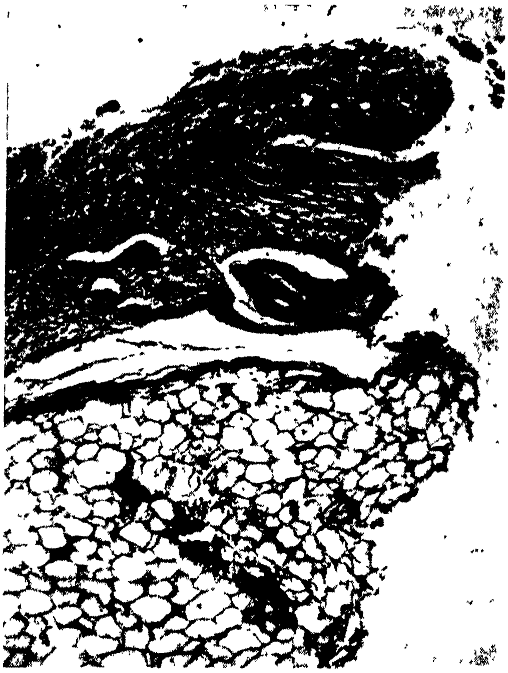


FIG. 678. *Meningeal lipoma* from region of the tuber cinereum, a portion of the latter, consisting of glial tissue containing nerve-cells and vessels, being seen in the upper half of the illustration. The lower part consists of a small mass of fatty tissue—one of several closely adjacent nodules, the largest of which measured 10 mm. in diameter. From a male aged thirty-seven. (W.E.H. case.) v. Gieson and hæmatoxylin. × 75.

(For further descriptions of some of the foregoing tumours, see pp. 298 and 316 *et seq.*)

From their investigations of **tissue-cultures** of **meningiomas,** Bland and Dorothy Russell,[3] in their series of 106 surgical specimens (14 of them submitted to tissue-culture), divide meningeal tumours into five groups in order of frequency, as follows :—

I.	Endotheliomatous,	corresponding to Bailey and Bucy's types (3) and (4).
II.	Fibroblastic,	,, ,, ,, type (6).
III.	Angeioblastic,	,, ,, ,, ,, (2).
IV.	Xanthomatous,	,, ,, ,, ,, (9) ?
V.	Myxomatous,	,, ,, ,, ,, (1).

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[1] *Loc. cit.*, p. 50, and also "Intracranial Sarcomatous Tumours of Leptomeningeal Origin," *Archives of Surgery*, 1929, **18**, 1359–1402.

[2] *Loc. cit.*, pp. 38, 50.

[3] "Histological Types of Meningiomata and a Comparison of their Behaviour in Tissue Culture with that of certain Normal Human Tissues," by J. O. W. Bland and Dorothy S. Russell, London Hospital, *Journ. Path. and Bact.*, 1938, **47**, 291.

The **meningotheliomatous** and the **psammomatous** forms—Bailey and Bucy's types (3) and (4)—constitute a continuous series, different parts of the same tumour often exhibiting **both** types and all intermediate admixtures or grades, this being also our own experience of these tumours. It is convenient, however, to be able to classify them in one or other of Bailey and Bucy's two groups, or to state that they are "intermediate forms."

Bland and Dorothy Russell regard Bailey and Bucy's **lipomata** of the meninges (as do we) as derived from embryonic rests or residues (Fig. 678). They regard the "**xanthomatous**" type (9) as a distinct variety; but our own experience with regard to it, as stated above, is that all degrees, slight and patchy, up to extensive and diffuse, of the "xanthomatous" change can occur as a **secondary** phenomenon in *any* of the meningiomatous tumours, especially where degenerative or hæmorrhagic changes have previously supervened—and that the **angioblastic process** is often associated or combined with the "xanthomatous," the two processes frequently taking place side by side, as illustrated in Figs. 659 and 660 on pp. 1084–5, for the original character of which tumour *see also* Fig. 669 on p. 1090. (Compare also the analogous (but non-neoplastic) process in Figs. 644–5 on pp. 1055–6: and Fig. 749 on p. 1161 and compare with note on p. 1263 *re* "xanthomatosis," primary and secondary.)

Teratomas occasionally occur. **Cysts** containing **cholesterol-crystals** are fairly common, mainly in connection with suprasellar tumours. For descriptions of these and of **cholesteatomas,** see pp. 350 and 817–18. **Meningoceles** are described on p. 1065 *et seq.*

TUMOURS OF THE BRAIN AND SPINAL CORD

Percival Bailey and Harvey Cushing, the modern pioneers of this important subject, make, in their classical book on "Tumours of the Glioma Group,"[1] the categorical statement that: "Of all organs of the body, with the possible exception of the uterus, the brain appears to be the most frequent seat of neoplastic disorders; and as many of the tumours of the brain are similar to or identical with those attacking the spinal cord and other parts of the nervous system, it is convenient to consider all of these together."

The problem of the origin of tumours in general is discussed on p. 281 *et seq.* In connection with the neoplasms of the nervous system it may, however, be emphasised that there appears to be evidence that certain of its tumours may arise **from embryonic "rests"** or **residues** (p. 283), and at likely sites may grow from surviving undifferentiated (and perhaps misplaced) cells of, say, primitive medullary epithelium, as in the case of medullo-epitheliomas and medulloblastomas[2]; but it appears equally likely that other tumours of nervous tissues are **anaplastic** and are developed by a process of what has been called "**de-differentiation,**" in which the mature cell recapitulates some part of its histogenesis and reverts to an earlier phase of its own development, as, for example, where adult glia-cells revert to the stage of the more primitive glioblasts and give rise to the malignant glioblastoma multiforme. From another point of view, this "de-differentiation" might be regarded as the **loss by the cells of their more recently-acquired characteristics.**

The modern terminology of the tumours arising from the various constituent parts of the nervous system appears complicated, but, if the histogenesis and general characters of its component cells—neuronal, glial, ependymal, and choroidal—be kept in mind and Percival Bailey's illustrative and explanatory diagrams on pp. 952 and 1098 consulted, it will be found, in theory at all events, if not always in practice, comparatively simple.

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[1] Bailey and Cushing, *loc. cit.*, p. 96. See note on p. 954 of this Chapter. (If it were our custom to "dedicate" the individual Chapters of our Textbook, I would dedicate this Chapter on "*Diseases of the Nervous System*" to the two Authors of this Book, in grateful appreciation of their work. W.E.C.D.)

[2] It is perhaps almost unnecessary to recall that the term "medullary" has here an **embryogenetic** significance, *i.e.*, pertaining to, or derived from, the neural or **medullary** plate, from which the nervous system is developed—more particularly in connection with the "**medulloblasts**" of the primitive neural tube from which neuronal and glial tissues are both derived. The word "medulla" was employed originally by the older anatomists to designate the *soft* contents of the bones. The **regional** term "medulla oblongata" was used to contrast that portion of the brain-stem with its continuation as the "medulla spinalis," the "spinal marrow" or spinal cord.

Bailey and Cushing (1926) have enumerated—exclusive of those of the membranes, vessels and connective tissue—some twenty varieties of normal cell composing the nervous system at the various stages of its development (Fig. 570, p. 952), and fourteen varieties of tumour derived from these cells ; but certain of the tumour-groups are closely allied and may be considered together. Bailey and Cushing do not claim completeness or finality for their work, and have themselves made suggestions for its simplification, but at the present time it forms the most useful basis for the investigation and description of tumours of the brain and spinal cord, whilst other apparently less complicated classifications so far put forward are found to break down and be unworkable in practice. Some of these tumours are composed of a single or at all events a predominating cell-type, but others may contain several or even a series of such types, for, as pointed out by Bailey, " these represent only transitory phases of a continuous development."

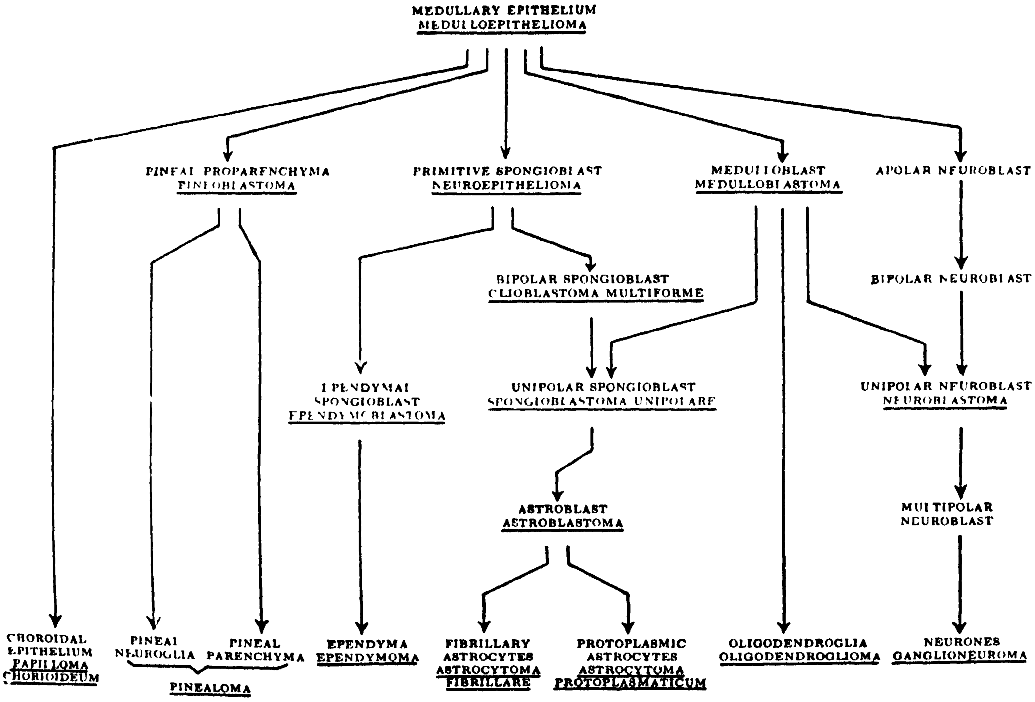
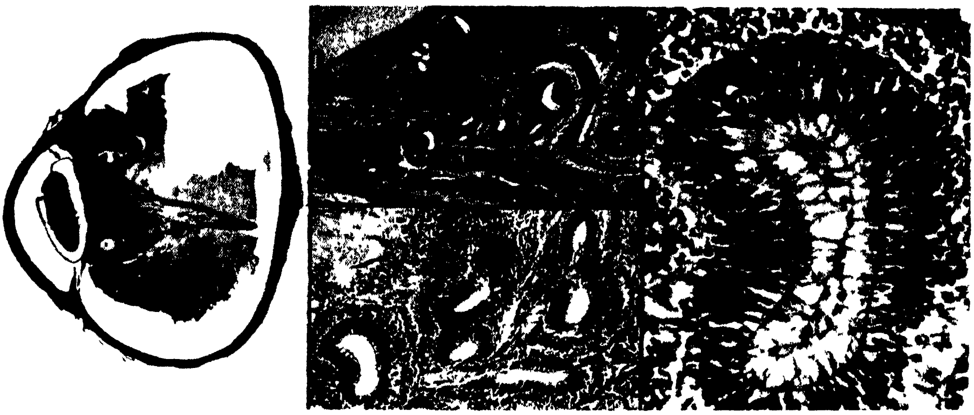


FIG. 679. *Scheme to relate types of gliomatous and neuromatous tumours* according to the predominant cellular constitution of each group (*cf.* Fig. 570, p. 952). (*Note.*—The term " glioblastoma multiforme " is now usually substituted for " spongioblastoma multiforme.") (By courtesy of Dr. Percival Bailey.)

Some such detailed classification of tumours of the nervous system is needful, not merely for purposes of diagnosis, but also for prognosis and treatment, and we shall deal with them under the following headings :—

1. Medullo-epithelioma and Neuro-epithelioma (p. 1099).
2. Medulloblastoma (p. 1099).
3. **Glioblastoma multiforme** (p. 1103).
4. Spongioblastoma or Glioblastoma polare (p. 1107).
5. Astroblastoma (p. 1108).
6. **Astrocytoma, Protoplasmic** and **Fibrillary** (p. 1108).
7. Oligodendroglioma (p. 1113).
8. " Ganglioneuroma " (Nerve-Cell Tumour—Neurocytoma and Neuroblastoma) (p. 1114).
9. Ependymoma and Ependymoblastoma (p. 1118).
10. Pinealoma and Pineoblastoma (pp. 848 and 1120).

(1) **Medullo-epithelioma** and **Neuro-epithelioma.** These are amongst the rarest of the tumours affecting the nervous system. Some writers distinguish between them, but it is not infrequently a difficult matter to determine in which of the two categories an individual tumour should be placed, and it is convenient to regard them as varieties at either extremity of a single group tending in varying degree to imitate, and sometimes closely to reproduce, the structure of the epithelium of the primitive medullary plate and neural tube (Fig. 570, p. 952 and Fig. 680 below). This group of tumours occurs especially in children in those portions of the brain in which the original medullary epithelium remains least differentiated, such as the roof- and floor-plates of the third and fourth ventricles : occasionally in the spinal cord, *e.g.*, in the sacro-coccygeal region (presumably from remnants of the medullary epithelium there) : and, slightly less infrequently, from the **pars ciliaris retinæ**—the retina being itself structurally part of the central nervous system. "Neuro-epitheliomas" have been described as occurring also in connection with **peripheral nerves,** such as the median or ulnar (pp. 1140 and 1143–4); but only with extreme rarity in the cerebrum. The tumours of both varieties tend to be highly malignant, and metastases from them may occur outside the central nervous system, a phenomenon found only exceptionally with other members of the glioma group. These tumours tend to reproduce the tube-like arrangement of the primitive spongioblasts around a central canal, sometimes with inner and outer limiting membranes (Fig. 680, D), and sections of these radially arranged cells thus show a characteristic **rosette-like** form, and in some instances even a "pseudo-glandular" appearance may be produced, in others a papilloma-like structure. In certain of the medulloblastomas and ependymomas (see below), a somewhat analogous but usually much more imperfect "rosette-like" grouping of the tumour-cells may be found.


(B) × 15.

(A) × 2½. (C) × 50. (D) × 200.

FIG. 680. *Medullo-epithelioma of pars ciliaris retinæ* in the eye of an infant. (A) Vertical sagittal section through eyeball showing the size and position of the tumour. (B), (C) and (D) Very low, low, and high-power views showing the reproduction by the tumour of the appearances of the primitive neural or medullary canal, with its cells and limiting membranes, as described in the text. The position and relations of the "tubule" shown in (D) can be seen in (B) and (C). (Reference should also be made to Figs. 192 and 570, pp. 357 and 952.) (By courtesy of Mr. Arnold Sorsby.) Hæmatoxylin and eosin.

(2) **Medulloblastoma.** This is a soft rapidly-growing malignant tumour of primitive type and characteristic symptomatology, occurring mostly **in children,** with its maximum incidence between the ages of five and ten years. It originates almost exclusively in the anterior part of the roof of the fourth ventricle in the region of the **vermis of the cerebellum.** Developmentally this

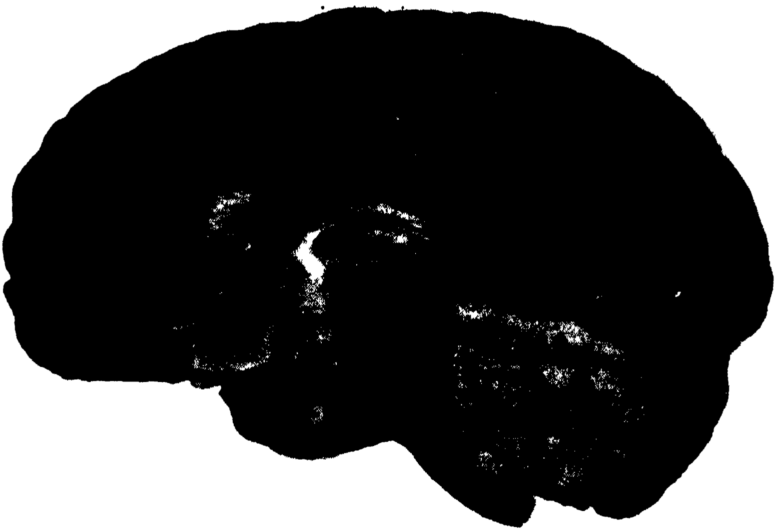


FIG. 681. *Medulloblastoma: large "mid-cerebellar tumour," in a boy aged five years,* in the roof of the fourth ventricle, expanding the cerebellum and causing moderate hydrocephalus, seen in the illustration as distended aqueduct, third ventricle and right interventricular foramen of Monro, and infundibulum. Near the foramen, some "seeding" of the tumour is seen on the ventricular wall (*cf.* Fig. 682, below.) (W.E.H. case.)

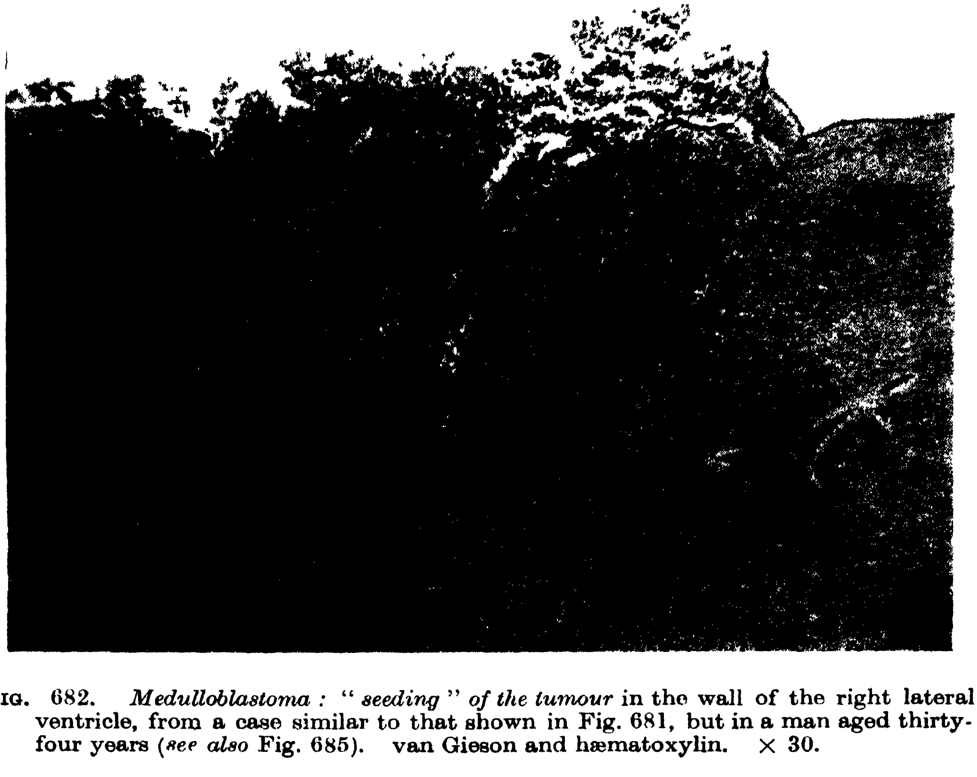


FIG. 682. *Medulloblastoma : " seeding " of the tumour* in the wall of the right lateral ventricle, from a case similar to that shown in Fig. 681, but in a man aged thirty-four years (*see also* Fig. 685). van Gieson and hæmatoxylin. × 30.

is the most ancient or primitive portion of the cerebellum and is concerned especially with the functions of walking and balancing, lesions situated in it causing what Bailey has therefore called the "palæo-cerebellar syndrome." The tumour is found only rarely elsewhere, a very few doubtful cases in the cerebral hemispheres of adults having been reported. These "mid-cerebellar tumours" infiltrate surrounding tissues and invade the cavity of the fourth ventricle,pushing their way into and distending it and the aqueduct and perhaps the third ventricle (Fig. 681). The interior of the cerebellum itself may be extensively destroyed, and the mid-brain may be invaded. When they invade the ventricles and also if they reach the surface of the brain, these medulloblastomas may spread, not only by continuity, but also by "seeding" at a distance, either in the ventricular system or in the subarachnoid space of both brain and cord (Figs. 681, 682 and 683).

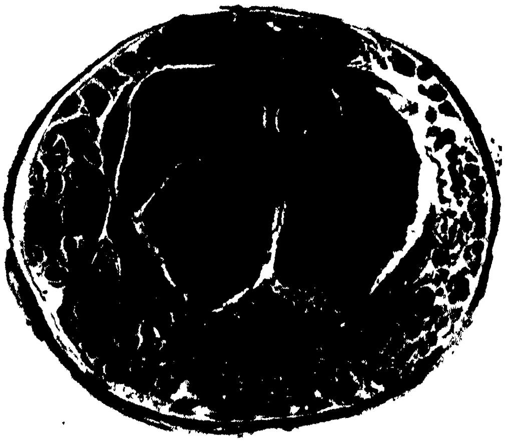
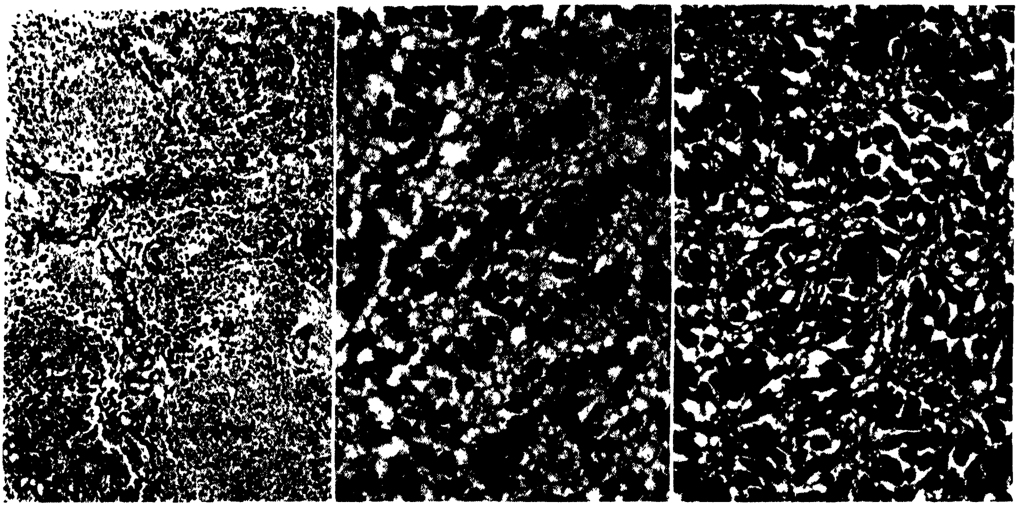


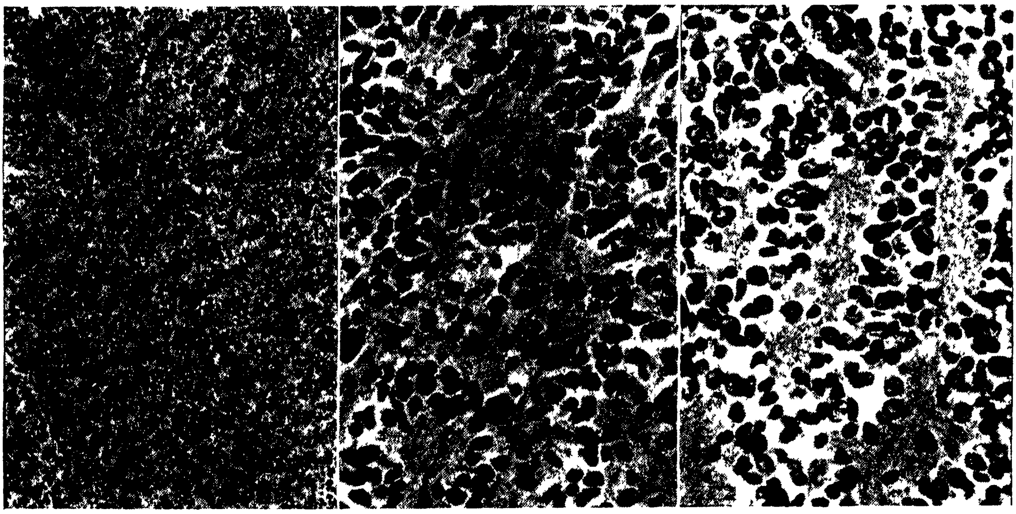
FIG. 683. *Medulloblastoma :* transverse section of the spinal cord of a girl aged thirteen years, showing invasion of the theca from above by a mid-cerebellar tumour similar to that illustrated in Fig. 681. Mallory's connective-tissue stain. × 3½.

Although, and perhaps because, they are thus so definitely primitive and malignant, they are distinctly radio-sensitive. On account of their usual site in the roof of the fourth ventricle, they often produce obstructive hydrocephalus. Microscopically, they are composed of plump irregularly ovoid or somewhat carrot-shaped undifferentiated cells, **medulloblasts,** with spherical or ovoid nuclei and scanty cytoplasm without processes. These cells are often closely and more or less irregularly arranged, but they not infrequently exhibit a mosaic pattern of pseudo-rosettes with no central cavity, but the tails of the cells pointing inwards, or again they may show a curved band- or wave-like grouping of their nuclei (Figs. 684–5). As the term implies, these "medulloblasts" are regarded as still possessing the potentiality of differentiating into either **glioblasts** or **neuroblasts,** and, in individual tumours, in addition to the usually more numerous **undifferentiated medulloblasts** themselves, varying admixtures of these two types of cell may be found (Fig. 686). Numerous capillary blood-



(A) × 85. (B) × 325. (C) × 325.

FIG. 684. *Medulloblastoma : a " mid-cerebellar tumour " in a boy aged nine years.* The low-power view (A) indicates the variability of the appearances in different parts areas showing " pseudo-rosettes " being seen at the top-right and lower-left corners, the details of which are shown in (C), *e.g.*, the " carrot-shaped " medulloblasts around fibrillary centres. A network of fine capillaries is often a characteristic feature, as in (A) ; whilst in (B) the tumour-cells are arranged in irregular " waves." Most of the cells are undifferentiated medulloblasts or are developing into glioblastic cells. A single neuroblast is seen at the lower-right corner of (B). (*Cf.* Figs. 685, C : 686, B and C : and 701 to 703, pp. 1115–16.) (W.E.H. case.) Hæmatoxylin and eosin.

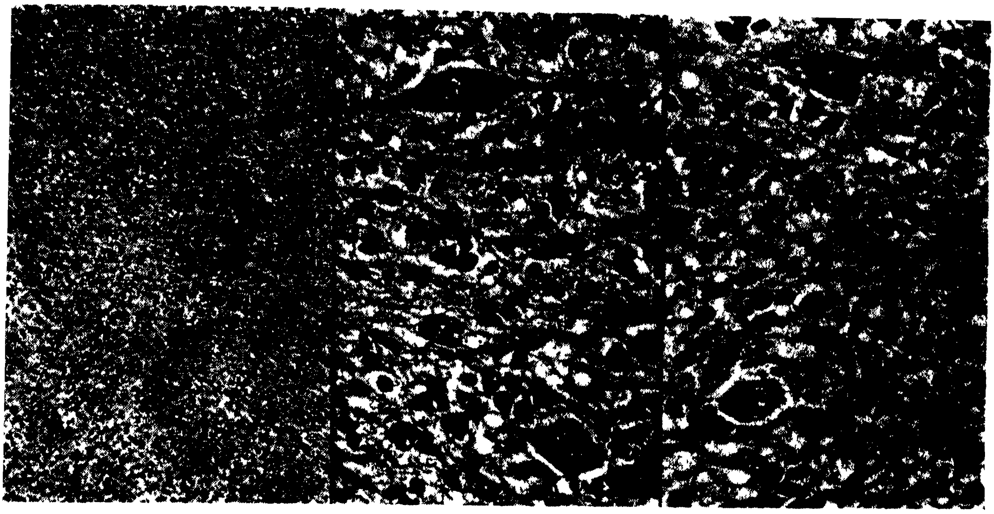


(A) × 85 (B) × 325 (C) × 325

FIG. 685. *Medulloblastoma : a " mid-cerebellar tumour " in a man aged thirty-four years* - the same case as illustrated in Fig. 682, these photomicrographs being from this " seeding " in the ventricular wall. The low-power view (A) shows the medulloblasts arranged in " pseudo-rosettes " and " waves," of which the high-power views (B) and (C) give further details, *e.g.*, some slight degree of differentiation of the bi-potential cells of the tumour into glioblasts and neuroblasts. (W.E.H. case.) van Gieson and hæmatoxylin.

vessels are, as a rule, present, and may be united with each other by a delicate spider-web network of collagenous fibrils.

Analogous cellular tumours of the **retina** (**retinoblastomas,** p. 315) and of



(A) × 85 (B) × 325 (C) × 3

FIG. 686. *Medulloblastoma: a "mid-cerebellar tumour" in a woman aged twenty-six years*, in which some of the bipotential cells have developed into definite *neuroblasts* and even into *neurocytes*; whilst the majority of the tumour-cells have remained in the form of *medulloblasts* and *glioblasts*. This tumour might therefore be termed a "*neuroblastic medulloblastoma*" or a "*medulloblastoma neuromatosum*." (*See* p. 1114, and compare with Figs. 700 to 704.) (W.E.H. case.) Hæmatoxylin and eosin.

sympathetic ganglia (p. 846) and also of the **suprarenal medulla** (pp. 845–7) are found.

(3) **GLIOBLASTOMA MULTIFORME.**[1] This is the common and rapidly-growing type of malignant tumour formerly known as "gliosarcoma." It is found mostly in the cerebral hemispheres of adults, its maximum age-incidence being in the decade between forty and fifty. Next to the astrocytomas, it constitutes the largest single group of gliomatous tumours. It is rapidly fatal, the average survival-period after the first appearance of symptoms being only about twelve months. Such tumours sometimes attain a very large size, infiltrating and destroying a large part of one or even of both hemispheres. On section, they present a much variegated appearance, with a mixture of pinkish-white tumour-tissue, the red and brownish-red of recent or of older and often extensive hæmorrhages, the opaque yellow and yellowish-white of necrosis, sometimes with the presence of ragged cavities or pseudocysts, and frequently an accompanying œdema of the surrounding brain-tissue into which the tumour merges with no distinct margin and no attempt at encapsulation by either glia or connective tissue. Often, however, the periphery of the tumour may be mapped out by a zone of vascular engorgement and hæmorrhage. There is usually pronounced flattening of the surfaces of the convolutions, and the probable site of a subjacent tumour can often be suspected from the broadening and perhaps discoloration of these and the obliteration, partial or sometimes even almost complete, of the intervening sulci. Such an area of brain-surface may have a "baggy" feeling on palpation, and there is often swelling and distortion of a large part or perhaps the whole

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[1] Originally described by Bailey and Cushing as "Spongioblastoma multiforme."

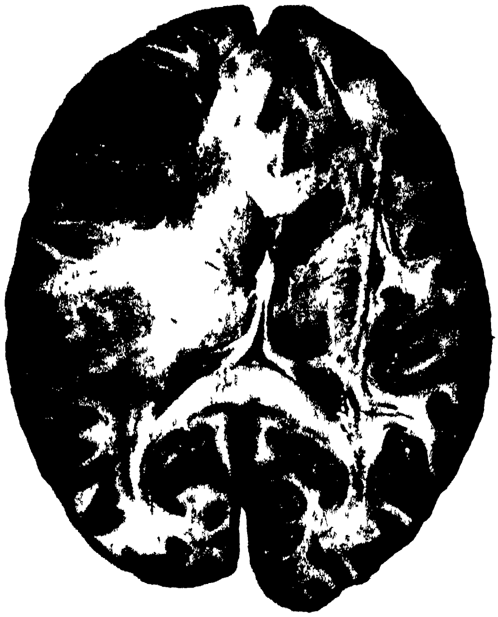

FIG. 687. *Glioblastoma multiforme* A medium sized example of this locally-malignant infiltrating tumour in left frontal lobe of a middle-aged female.

of one hemisphere, with corresponding displacement of the mid-plane of the brain towards the opposite side, and compression and distortion not only of the opposite hemisphere but also of other more distant parts. In other cases, however, there is rapid invasion and infiltration of the surrounding tissues rather

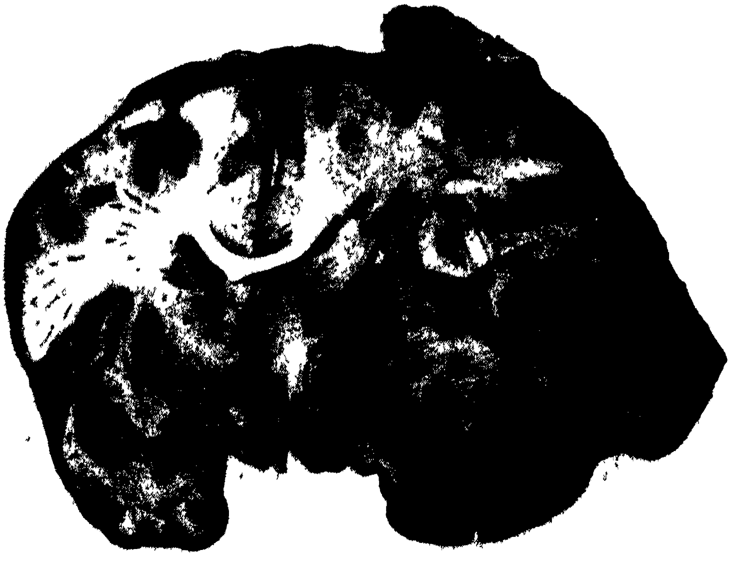

FIG. 688. *Glioblastoma multiforme.* A large tumour infiltrating the right temporal lobe in a man aged sixty-six. A decompression-operation for the relief of pressure has caused some herniation of the tumour outwards. Some parts of the tumour had the structure of a polar spongioblastoma, but most of the mass showed further reversion to the more malignant glioblastoma multiforme (*see* Fig. 679, p. 1098). (W.E.H. case.)

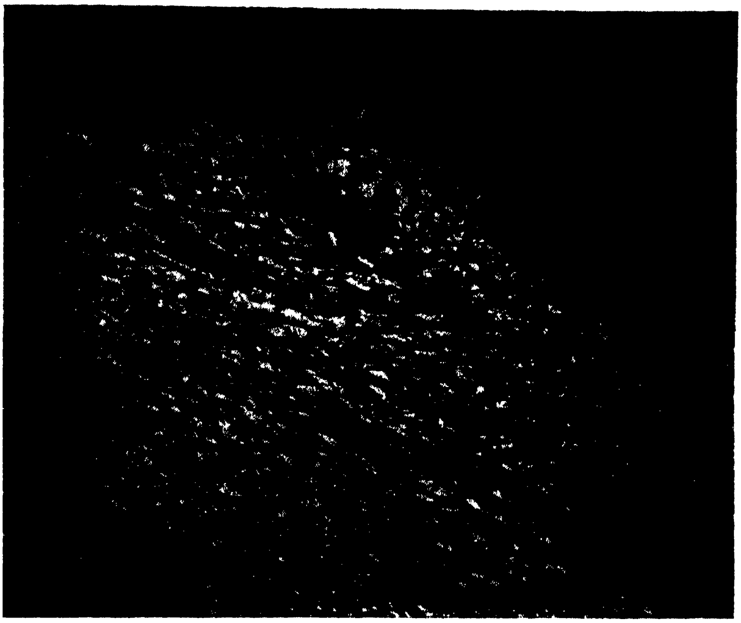

FIG. 689. *Glioblastoma multiforme.* Low-power view to illustrate the variability of the component cells, which have been impregnated by del Rio-Hortega's silver-carbonate method. The prevailing cells are spindle-shaped or polar cells, but with a tendency to formation of astroblasts and astrocytes. The intercellular fibrillary material consists of the frayed-out ends of the spindle-shaped cells. A few giant tumour-cells are also shown. In the upper right corner, there is an area of necrosis, around which the cells are arranged in the form of a "palisade." 85.

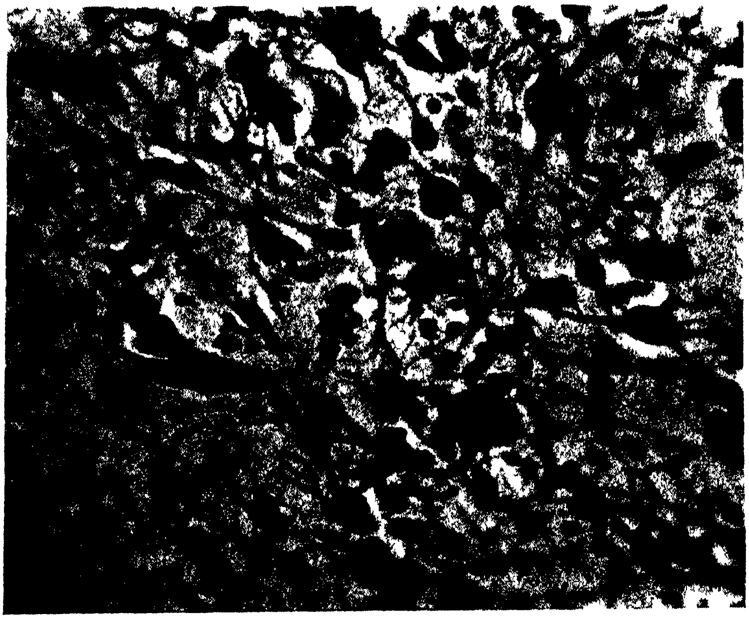

FIG. 690. *Glioblastoma multiforme.* Higher-power view of the same showing the variety and variability of the cells, from which the tumour derives its name. Hortega's silver-carbonate method. × 300.

than the pushing of them aside, in other words, such tumours may be either **invasive** or **expansile,** or a combination of these characteristics in varying proportions.

Microscopically, the glioblastoma multiforme is a cellular tumour [1] in which, as the name implies, the cells exhibit great diversity in size, shape and arrangement, and often show numerous and perhaps abnormal mitotic figures. The cells are usually small, with small spherical or ovoid nuclei, but often intermingled with larger and more irregular cells and sometimes with giant-cells—their nuclei often multiple or perhaps multilobed and complex, and their cytoplasm abundant and plasmodial. Not infrequently, the prevailing cell tends to be spindle-shaped, and hence these tumours were previously regarded as related to the spindle-celled sarcomas. Wide areas of intermingled degeneration, necrosis and hæmorrhage are of common occurrence. Phagocytic cells may be numerous, englobing fat and debris—the so-called " foam-cells " or " compound granular corpuscles " (*cf.* Figs. 644–5 and 659–660, pp. 1055–6 and 1084–5) derived from the mesoblastic microglial cells and also from the endothelial cells around or lining vessels—as well as hæmatogenous leucocytes, both mononuclear and polymorphonuclear. Attempts at repair, with the formation of areas of imperfect granulation-tissue, may occur. Numerous blood-vessels are usually present, sometimes proliferating in " glomeruloid " masses, the individual vessels being thin-walled, with no muscular coat, easily ruptured and thus readily giving rise to hæmorrhage, and also often becoming thrombosed and containing an excess of polymorphs. In the immediate neighbourhood of the blood-vessels, the tumour-cells may be better nourished and less liable to undergo necrosis, and such surviving zones may simulate the appearance of a so-called

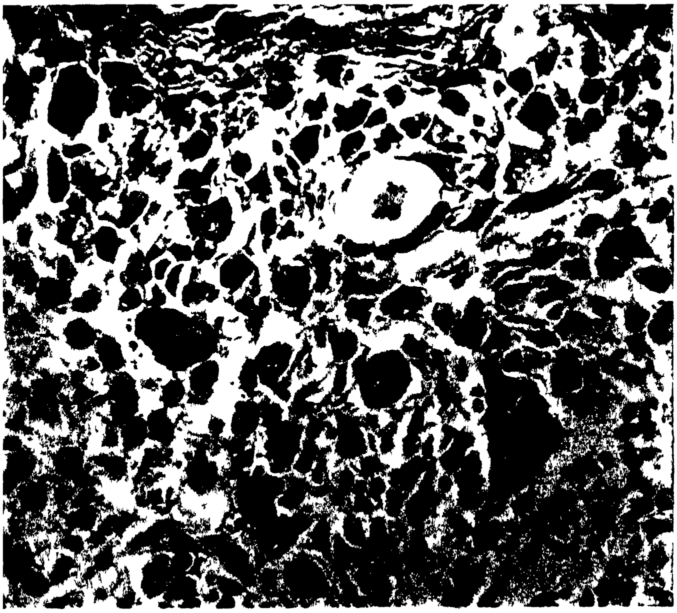

Fig 691 *Glioblastoma multiforme* High power view of another tumour showing great irregularity in the size and shape of the tumour cells, some of them large and multinucleated. Hæmatoxylin and eosin × 300.

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[1] For the characters of these cells in cell-culture, *see* p. 1126.

"perithelioma." In these perivascular zones and also round the borders of necrotic areas, the tumour-cells not infrequently show parallel grouping or "palisading" (Fig. 689). Towards and at the periphery of the growth, surviving glial, nerve-cell and nerve-fibre elements of the invaded tissues may have become surrounded and included among the tumour-cells, and the degenerative and reactive changes in them add to the general complexity of the histological picture.

(4) **Glioblastoma** (or **Spongioblastoma**) **Polare** or **Piloid Astrocytoma.**[1] These are tumours composed especially of fusiform cells which Bailey regards as unipolar spongioblasts. They tend to occur in the mid-line of the brain from optic chiasma in front to medulla posteriorly, and are capable of attaining a large size. They account for many of the gliomas of the optic nerves, chiasma, tracts and thalamus; and, from compression or involvement of the hypothalamus, may produce the characteristic syndrome referred to that region, *e.g.*, adiposity, polyuria, somnolence, etc. (Fig. 595, p. 989). Others are found in the mid cerebellar region, and all are tumours mainly of childhood or early adult life.

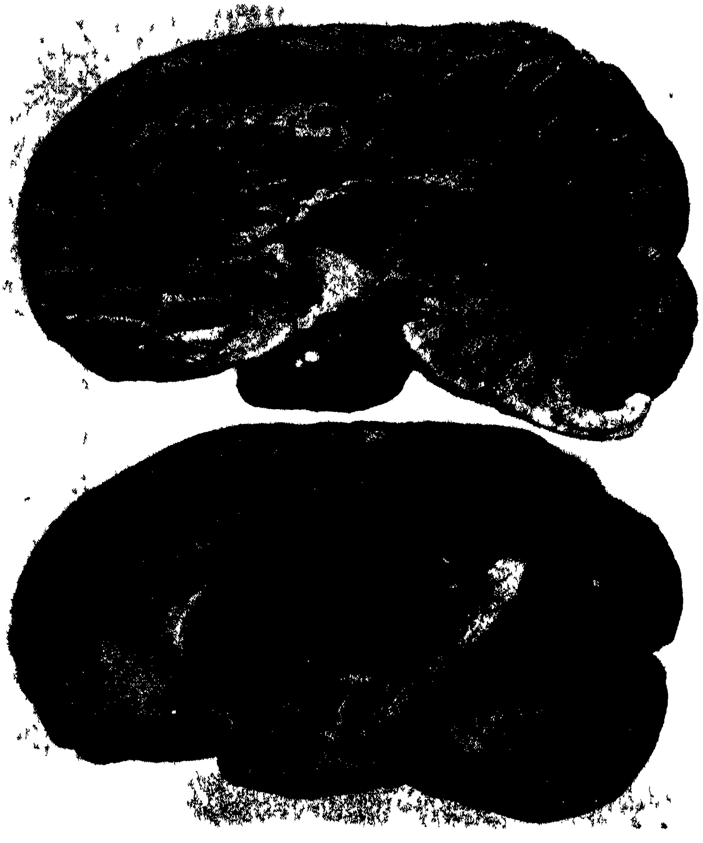

FIG. 692. *Large polar glioblastoma of the right optic thalamus* in a boy aged nine years, with only an eight weeks' clinical history.
(Upper) Mesial sagittal section showing a small portion of the tumour projecting across the middle line in the upper and posterior part of the third ventricle.
(Lower) Section parallel with and about 35 mm. external to the upper illustration through the main mass of the tumour. (W. E. H. case.)

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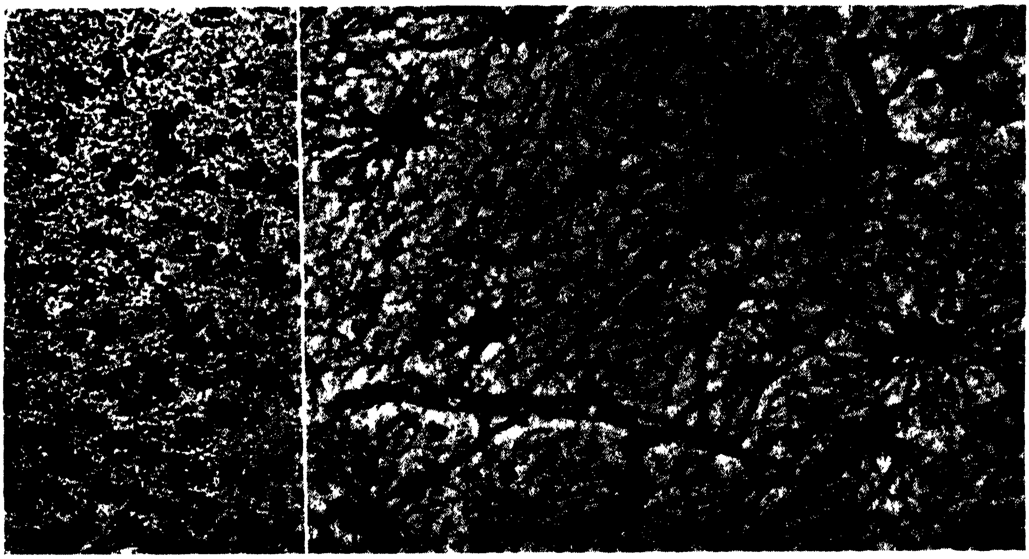
[1] "Piloid," hairlike, from Greek, πῖλος, *pīlos*, a compressed feltwork of wool or hair (πιλεῖν, *pīlein*, to compress) and πιλο ειδης, *pīlo eidēs*, like felt.

Microscopically, these neoplasms show a superficial resemblance to acoustic neurofibromas, but special staining-methods demonstrate the "wire-like" processes of the **bipolar** and the tadpole-like **unipolar spongioblasts** found present in varying admixtures. Mitotic figures are rare, and these growths tend to be less vascular than the more malignant glioblastoma multiforme; but intermediate forms are not uncommon. Wilder Penfield[1] (1932) regards these tumours as intermediate between the spongioblastoma multiforme and the astrocytoma, a view which is consistent with their comparatively benign clinical characters; and he has therefore suggested the term "piloid astrocytoma" for them. Dorothy Russell and Bland (*see* p. 1125), from their investigation of these tumours by cell-culture, come to a similar conclusion.

(5) **Astroblastomas** are intermediate between the glioblastomas and astrocytomas, being firmer and paler and showing less tendency to hæmorrhages than the former, but softer and rather more anaplastic than the more benign and slow-growing astrocytomas. They show no definite margin and merge imperceptibly into the surrounding brain-tissue. The **astroblasts** of which they are composed have usually somewhat triangular or polygonal bodies with fairly abundant cytoplasm, from one pole of which a stout "vascular process" or "sucker-foot" passes to an adjacent blood-vessel, whilst from the opposite pole only a few imperfectly developed processes originate. These cells can be distinguished from pyramidal nerve-cells, to which they have a superficial resemblance, by gold-impregnation methods, the main vascular process, unlike the axon of the nerve-cell, being attached to a neighbouring capillary by its foot-like expansion. The chromatin is arranged in numerous masses evenly distributed throughout the nuclei, which do not possess the prominent nucleoli characteristic of nerve-cells. No glial fibrillæ are found in the cell-body or its processes.



(A) × 350. (B) × 350.

FIG. 693. *Protoplasmic-celled astrocytoma.* A biopsy-specimen from the right frontal lobe of a woman aged fifty-eight. (A) A thick, fresh-wet toluidin-blue film showing the characterless appearance of the tumour-cells when stained by this method, as compared and contrasted with (B) a frozen section, under the *same* magnification, showing the astrocytes with their numerous processes, many of them thickened and with their "vascular feet" attached to a small blood-vessel—demonstrated by Bielchowsky's silver-impregnation method. (W.E.H. case.)

(6) **ASTROCYTOMAS, Protoplasmic** and **Fibrillary.** Astrocytomas may occur in practically any part of the central nervous system. The **protoplasmic-celled**

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[1] "Cytology and Cellular Pathology of the Nervous System," New York, 1932, II, 455.

tumours are found mostly in the cortical grey matter : those of **fibrillary** type in the white matter and also in relation to the subpial and subependymal glial-tissue layers of brain-surface and ventricular walls respectively. Taken together, these two varieties of astrocytoma constitute the largest single sub-group, *i.e.*, about a quarter to a third, of all primary brain-tumours, of which they—more particularly those of fibrillary type—are amongst the most slow-growing and benign. Even apart from any surgical interference, they may present a clinical history of many months and even years, as contrasted with the much shorter survival-period of glioblastoma-multiforme patients.

The **protoplasmic-celled astrocytomas** are found chiefly in the cerebellar cortex of children of from about five to fifteen years of age, and in the cerebral cortex of adults in the third and fourth decades of life. Both varieties of astrocyte may be demonstrated by Cajal's gold-sublimate method, and, with this and other special methods, the protoplasmic astrocytes are found to contain *no* glial fibrillæ either in the cell-body or in its much-branching processes (*see* key-diagrams, Figs. 570 and 679, pp. 952 and 1098), hence tumours of this variety tend to be softer than the slow-growing and benign **fibrillary astrocytoma,** in which the cells and their numerous long processes contain fibrillæ, constituting the "*glioma durum*" or "simple glioma" of the older writers. Its smooth homogeneous-looking pale greyish or yellowish-white cut surface often varies but slightly in appearance and is scarcely distinguishable from the surrounding white matter into which the margin of the tumour gradually

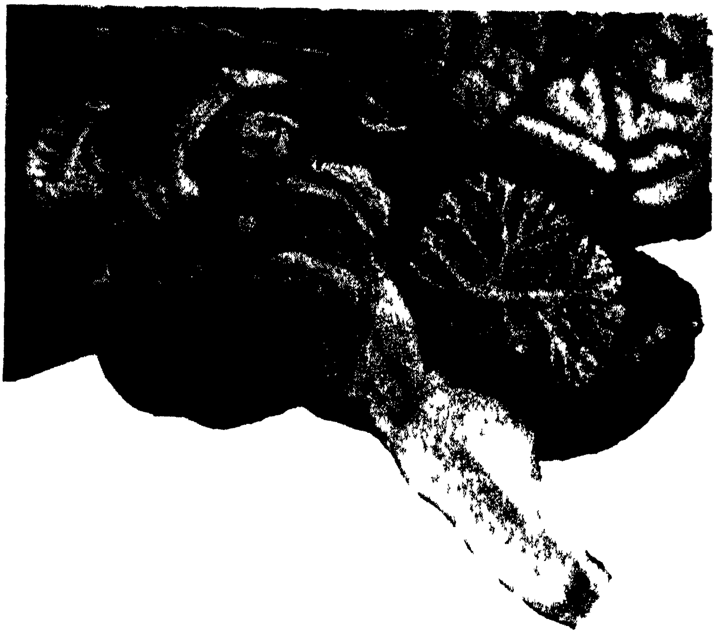

FIG. 694. "*Gliomatosis*" *of the medulla* in a woman aged fifty-five years Note the diffuse club like swelling in the lower part of the medulla and upper part of the cervical region of the cord a rarer localisation than in the pons. The valve-like compression of the ependymo pial foramina between the swelling and the under aspect of the cerebellum has led to the production of some degree of internal hydrocephalus. (W.E.H. case.)

merges. On palpation, however, a slight but appreciable difference in consistence in the fibrillary type, usually in the direction of increased firmness, is felt, though some of the protoplasmic-celled tumours may be softer than the surrounding brain-tissue.

It is sometimes a difficult matter to decide whether certain widespread **proliferations of glia,** many of them apparently congenital in origin, are to be regarded as neoplastic or non-neoplastic in nature. Until our knowledge of these processes is more complete, "**gliosis**" and "**gliomatosis**" are convenient non-committal terms for such conditions —for example, the diffuse form of gliosis seen occasionally in the pons (and known to the older writers as "*hypertrophy*" of the pons), more rarely in the medulla or elsewhere (Fig. 694, p. 1109). Analogous local proliferations of glia are seen in some of the congenital "**multiple-tumour syndromes,**" such as tuberous sclerosis (p. 1134) and certain cases of central neuro-fibromatosis (p. 1135). In the former of these, an astrocytic glioma, usually multiple, is occasionally found in the retina (Fig. 695).

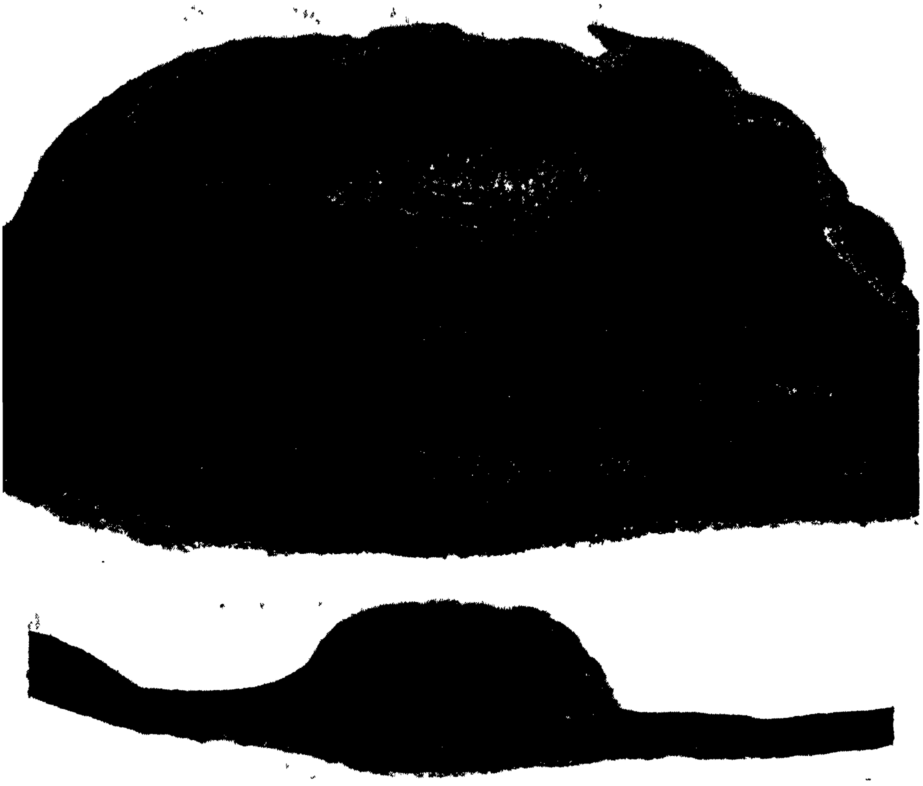

FIG. 695. *Glioma of retina.* The rare *fibrillary astrocytoma* found as part of the *tuberous-sclerosis syndrome* in a girl aged nineteen years. (By courtesy of Mr. Lindsay Rea.) Hæmatoxylin and eosin. × 30 and 100 respectively.

Both varieties of astrocytoma, probably on account of their comparative non-vascularity and scanty blood-supply, often show the development of degenerative **pseudocystic cavities,** single or multiple, usually with smooth and often firm well-defined walls, and containing clear yellow highly albuminous fluid. Occasionally, and especially in the **cerebellar tumours of children,** such a **cyst** may slowly increase to a considerable size, and the tumour itself may persist only locally in some part of the wall of the cavity as the so-called "**mural nodule,**" surgical removal of which, along with the rest of the cyst-wall, is essential to permanent cure.[1]

Microscopically, astrocytomas are composed chiefly or wholly of the two adult types of astrocyte and their processes, illustrated in Bailey's diagram (Fig. 570, p. 952, and Figs. 693 and 697, pp. 1108 and 1112).[2] Either type alone, or varying admixtures of both, are found in individual tumours. Both varieties of cell send one or more "vascular processes" or "sucker-feet" to adjacent blood-vessels and thus they may come to be arranged somewhat radially around the vessels (*see* Figs. 693 and 697), though this is less characteristic of them than of the astroblastomas. As indicated in these illustrations, special staining- or impregnation-methods are required for the demonstration

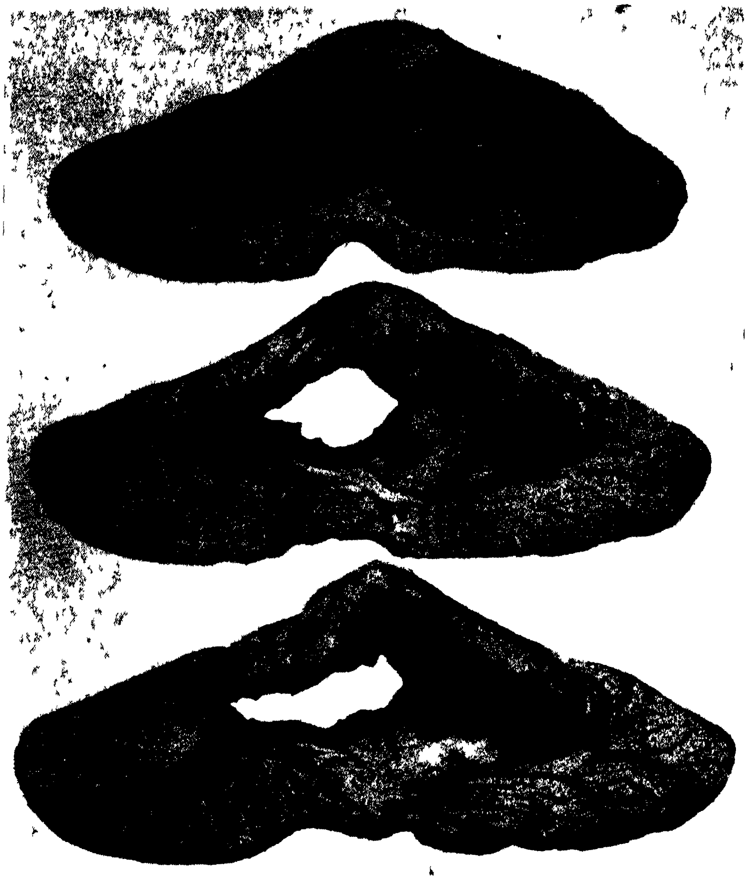

FIG. 696. "*Cerebellar cyst*" in a female patient aged twenty years: series of horizontal sections through a cavity which has developed in connection with a gliomatous tumour—*an astrocytoma*—(the pale area) into and around which hæmorrhage has occurred. Contrast this with the "angiomatous cyst" characteristic of Lindau's syndrome shown in Fig. 719 on p. 1131. (W E H case.)

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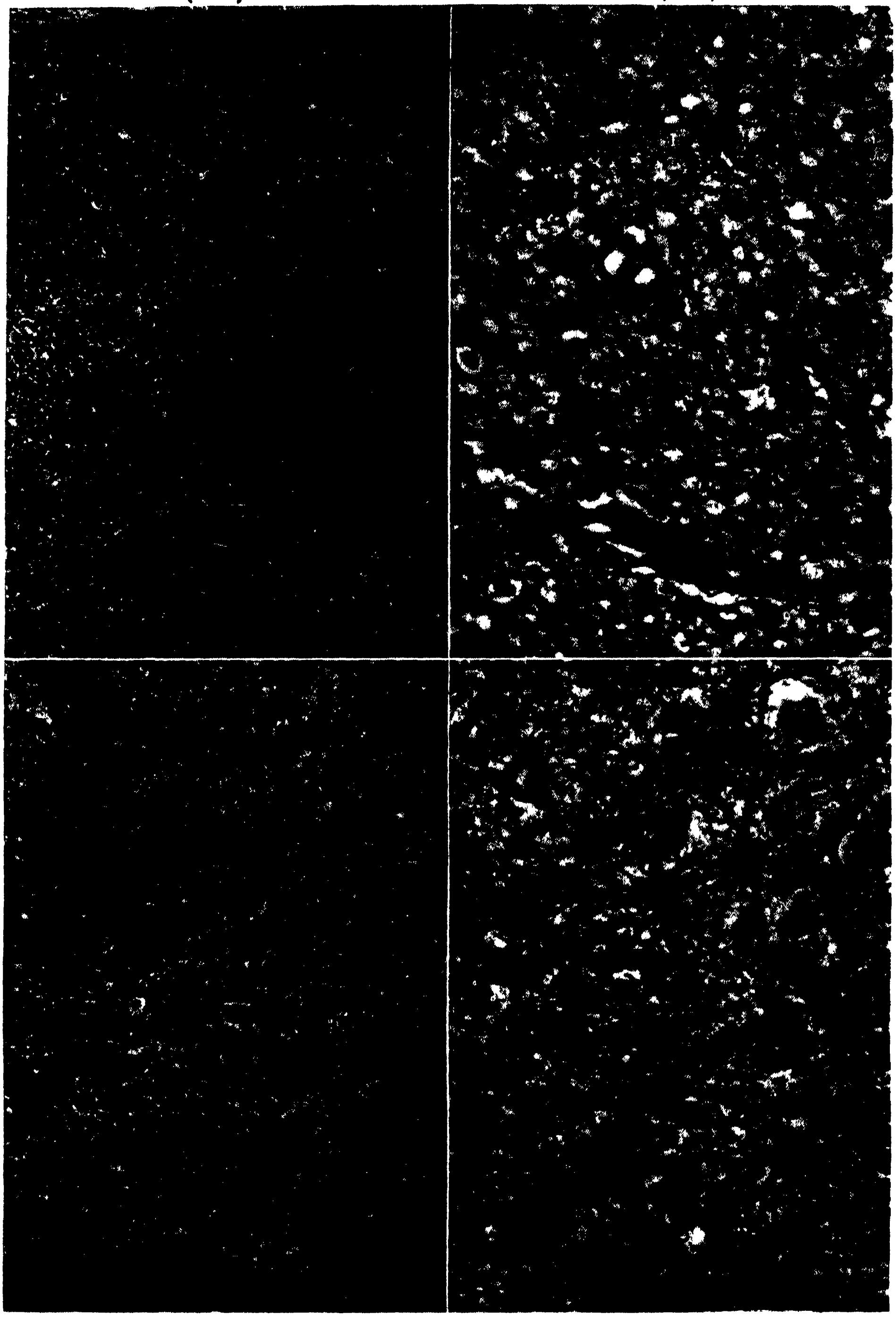
[1] For a description of the analogous variety of "cerebellar cyst" containing an angiomatous "mural nodule" found in Lindau's disease, *see* p. 1131.

[2] For the characters of the cells of this tumour in cell-cultures, *see* p. 1127.

(A.1.) × 85. (B.1.) × 350



(A.2.) × 85. (B.2.) × 350.

FIG. 697. *Fibrillary astrocytoma* of right frontal lobe: biopsy-specimen from a female aged thirty-three. (A.1.) and (B.1.) are low and high powers respectively of paraffin sections stained with hæmatoxylin and eosin. (A.2.) and (B.2.) are frozen sections of the *same* area impregnated by Cajal's gold-sublimate method for glia. These preparations show the advantages of employing *impregnation-methods* and *frozen sections* for the demonstration of the tissues and tumours of the nervous system. The irregular neoplastic astrocytes, with their branching processes and "vascular feet" are best seen in (B.2.). (W.E.H. case.)

of these "sucker-feet" and other cytoplasmic processes of astrocytes and of the specific glial fibrils contained in the fibrillary variety of these cells (*see* Percival Bailey's diagram, Fig. 570, p. 952). The blood-vessels themselves may be scanty and scattered, nourishing the cells in their immediate neighbourhood more efficiently than in the more distant intervening areas in which degenerative and necrotic changes may therefore occur, leaving zones of surviving tumour-cells immediately around the vessels. As in other varieties of glioma, transitional and mixed forms of tumour are common, and various degrees of reversion to astroblastoma and glioblastoma may supervene, especially after incomplete surgical removal.

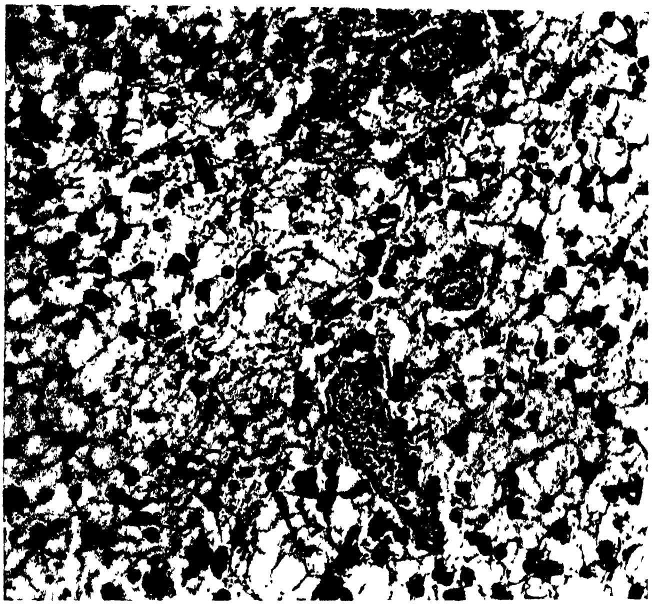


FIG. 698. *Fibrillary astrocytoma* of frontal lobe, showing branching glial cells, which, if impregnated by Cajal's method, would have shown astrocytic forms like those seen in Fig. 697 (B.2). Several thin-walled blood-vessels are seen in the section. Hæmatoxylin and eosin. × 250.

(7) **Oligodendroglioma.** This, like the astrocytoma, is one of the slow-growing tumours. It is usually composed of fully differentiated oligodendroglial cells (p. 955) and is found almost exclusively as a subcortical tumour in the white matter of the cerebral hemispheres of adults, with maximum incidence in the fifth decade of life. It is rare in the cerebellum and in children, but it occurs occasionally as a mid-line tumour in connection with the third[1] or fourth ventricle or the cerebral aqueduct. To the naked eye, these tumours are pink or reddish-grey, firm, with a fairly distinct margin, but no actual formation of a capsule around them. Although usually comparatively non-vascular, they may show hæmorrhages, but the formation of pseudocystic cavities is exceptional. One of their most important and characteristic features is the occurrence in them of patches of **calcification,** by which their presence can be detected on X-ray examination, such calcification following upon hyaline and lipoid degeneration in cells and vessels.

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[1] "Oligodendroglioma of Floor of Third Ventricle," (with illustrations), by W. E. Carnegie Dickson. *Proc. Roy. Soc. Med.* (Section of Neurology), 1926–7, p. 393: and *Brain* (no illustrations), 1926, **49**, 578.

Microscopically, the typical picture in paraffin-sections is one of numerous small and evenly distributed spherical nuclei, deeply stained, but surrounded by a zone of cytoplasm staining so poorly by ordinary methods as to be homogeneous-looking, the cell-bodies showing no definite outline, often hyaline and tending to coalesce with their neighbours, an appearance which has been likened to that seen in the transverse sections of some woody plants. It is difficult to demonstrate the few feeble processes of these cells even by special impregnation-methods in frozen sections, probably owing to their destruction by the rapid occurrence of autolysis unless the tissue has been immediately and carefully fixed. Hence this type of tumour has been recognised only comparatively recently as a member of the glioma-group.[1] Mitotic figures are rare, but after incomplete surgical removal the tumour may take on more rapid growth. Intermediate forms between oligodendrogliomas and astrocytomas and reversion to some of the more primitive types of glioma have been described.

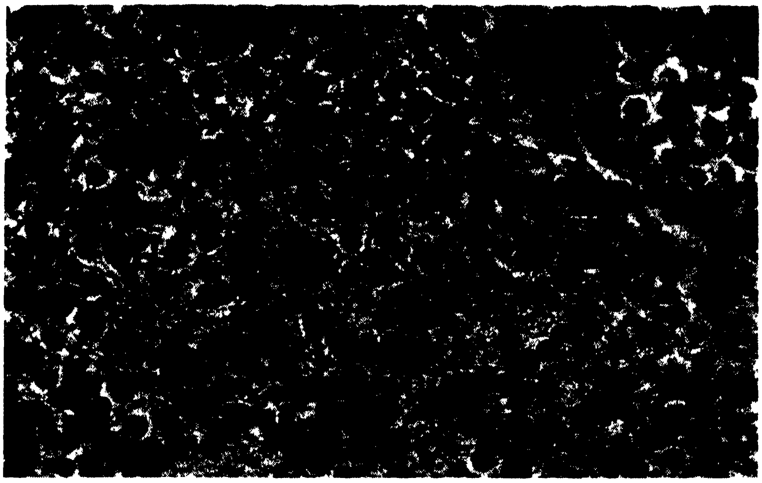

FIG. 699. *Oligodendroglioma* removed by operation from a man aged thirty-nine years: high-power view showing character of the cells (*see* text and *cf.* also Fig. 570, p. 952). A section of a small degenerated vessel and a calcified particle are also seen. (By courtesy of Mr. F. W. Willway and Dr. A. L. Taylor, Bristol General Hospital.) Hæmatoxylin and van Gieson. × 400.

(8) **Nerve-Cell Tumours.** The earlier developmental cells of the nervous system in general are bipotential, *i.e.*, may give rise to cells of either the glial or the nerve-cell series (p. 954). In comparatively rare instances, the medulloblasts of a medulloblastoma may differentiate into **neuroblasts** in sufficient numbers to justify the use of the descriptive term "**medulloblastoma neuromatosum,**" or, if these cells are numerous or even come to outnumber the medulloblasts and glioblasts, the tumour may be called a "**neuroblastoma,**" by some writers called a "ganglioglioblastoma," or, if composed of more mature cells, a "ganglioglioma."

Of less rarity, though still uncommon, are the mature-celled "**true neuromas**" of Virchow, or, as we shall call them here, the **neurocytomas,** as distinguished from the more primitive **neuroblastomas,** to which we have just referred, and in connection with which *see also* pp. 315 and 1101. In Percival

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[1] For the characters of the cells of these tumours in cell-cultures, *see* p. 1128

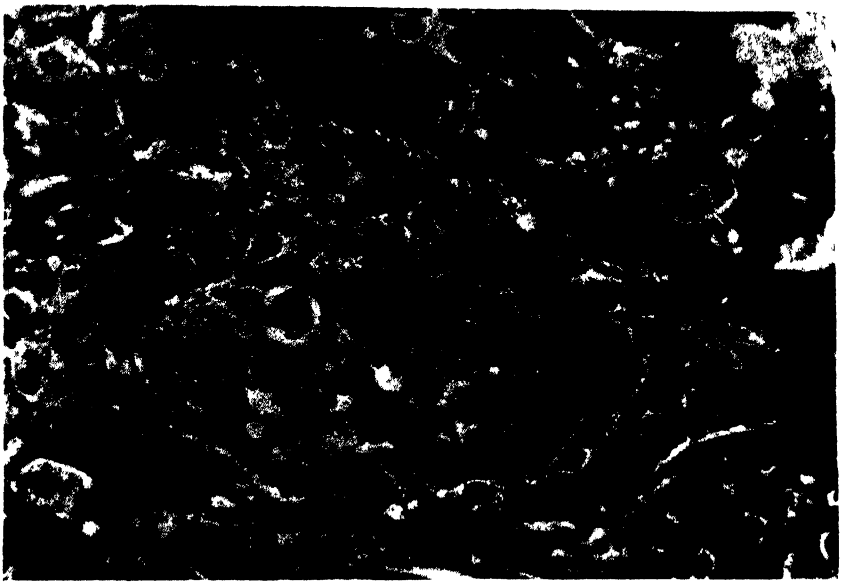

FIG. 700. *Neuroblastoma, developing at parts into a neurocytoma* : The form of nerve-cell tumour composed especially of the smaller polygonal *neuroblasts*, some of which tend to form proliferating groups : amongst which one cell, or sometimes several cells, become enlarged to form a prominent *nerve-cell* with vesicular nucleus containing a prominent nucleolus (*see* Fig. 703). From a tumour of a second lumbar spinal root in a man aged forty-five years. (W.E.H. case.) Mallory's stain. × 400.

FIG. 701. *Neuroblastoma* : Paraffin-section of biopsy-specimen from a male aged nineteen. The tumour, from the right post-Rolandic area, shows what appear to be bi-potential medulloblasts developing into neuroblasts (the larger cells with vesicular nuclei containing prominent nucleoli), and the smaller medulloblasts, single or grouped round the neuroblasts, and sometimes round the vessels to form glioblastic cells, *i.e.*, a "medulloblastoma neuroblastomatosum," which, in the cerebral hemispheres is a tumour of extreme rarity. (Compare Fig. 702.) Methylene blue. (W.E.H. case.) × 400

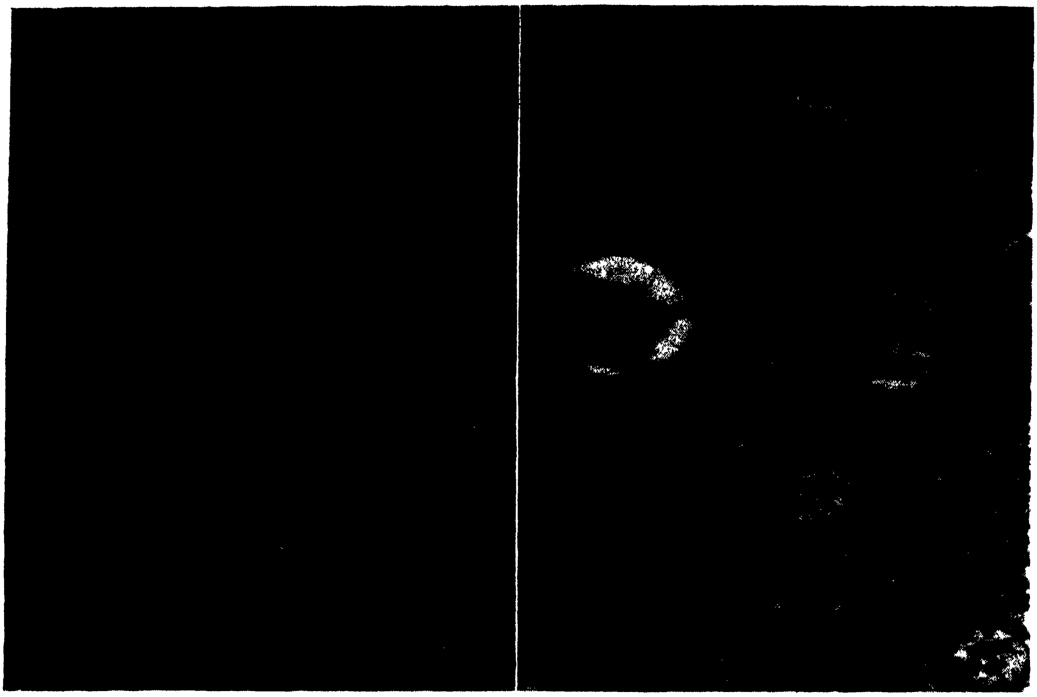
(A) (B)

FIG. 702. *Neuroblastoma, developing into a neurocytoma* (A) Paraffin-section from the same biopsy-specimen as Fig. 701, showing the neuroblasts developing into neurocytes and sometimes remaining still partially fused or "plasmodial." (B) An area of the tumour in which the neurocytic element predominates over the neuroblastic. (W.E.H. case). Methylene blue. × 1,000.

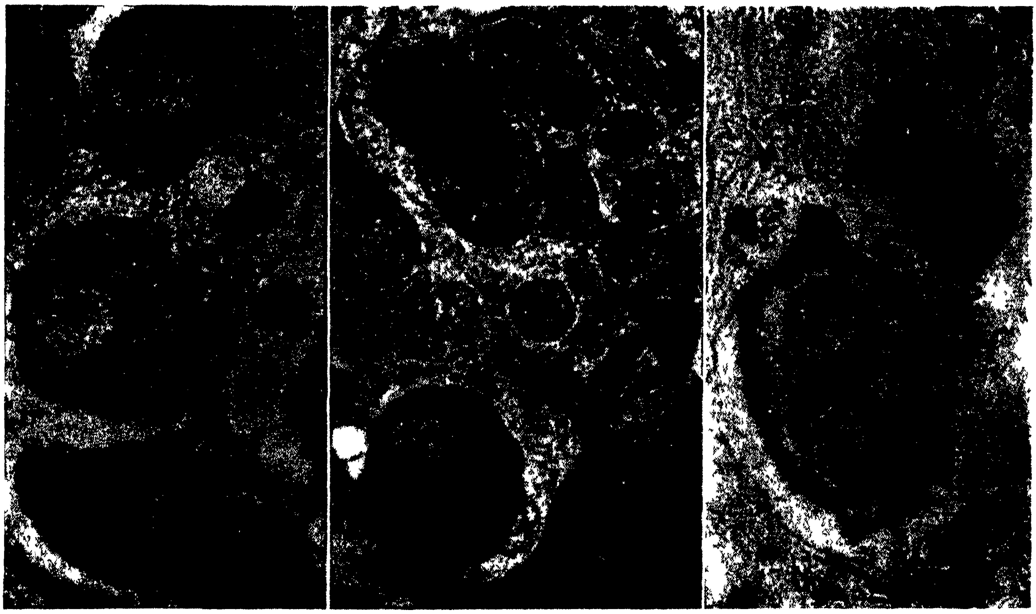
(A) (B) (C)

FIG. 703. *Neurocytoma:* Some of the large neoplastic nerve-cells from the same case as Figs. 700 and 704, under the oil-immersion lens. (A) Stained by Nissl's method to show the abnormal chromaphil cytoplasmic granules present in some of the tumour-cells. (B) A group of neuroblasts (the smaller cells), some of which have enlarged to form neurocytes or so-called "ganglionic cells." (C) One of the latter with three nuclei. (W.E.H. case.) Nissl's methylene-blue method. × 1,250.

Bailey's schematic table on p. 1098, it will be seen that the term "**ganglioneuroma**" is given to denote the tumour corresponding to the fully-formed "*neurone*" in the diagram (Fig. 679, p. 1098)—and it is so used by many writers—the word "*ganglion-cell*" being here employed as synonymous with "*nerve-cell*" in general. A certain element of confusion is, however, apt to arise from the fact that these tumours are found particularly in, and arising from, the nerve-cells of the *ganglia* upon cranial, spinal or autonomic nerves ; and, in order to avoid the misconception that these only are included in the term "ganglioneuroma," and as the word "neuronoma" is not in general use, we shall ourselves employ the terms "**neurocytoma**" and "**neuroblastoma,**" as above defined. True neuromas are found occasionally on peripheral nerves and in the sympathetic nervous system (including the suprarenal medulla, Fig. 492, p. 846), as well as in the ganglia on spinal and certain of the cranial nerves, and more rarely in the skin or internal organs : and—perhaps most rarely of all—in the central nervous system itself, in which "ganglioneuromas" (by some called "gangliogliomas") have been described as occurring in the region of the tuber cinereum and infundibulum, pineal body, cerebellum and medulla. These neurocytomas are relatively benign and consist of fully-developed **neurones,** *i.e.*, nerve-cells, with large vesicular nuclei (usually single, but occasionally two or even more in number, and each containing a prominent nucleolus, but only

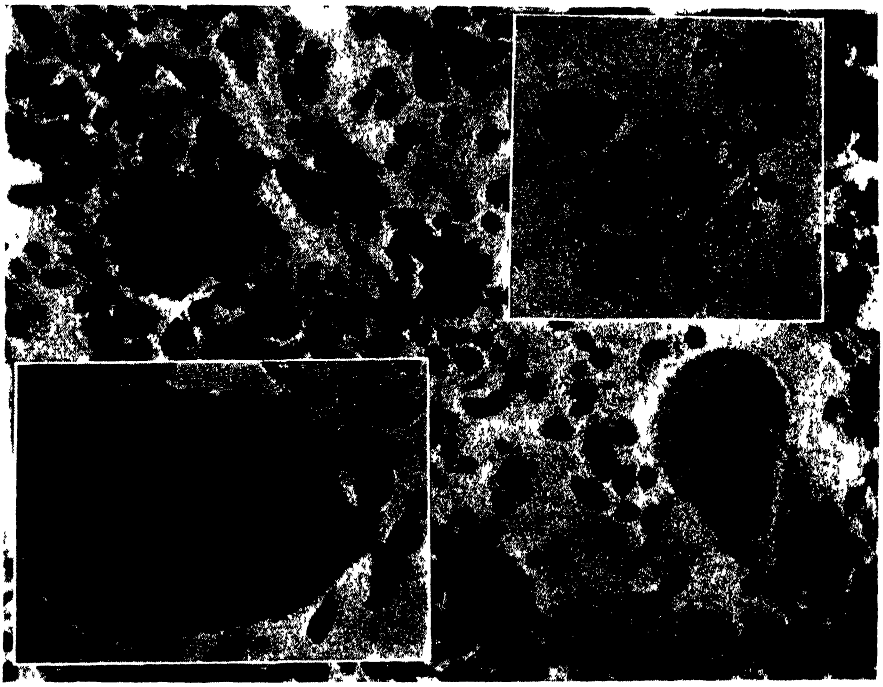

FIG. 704. *Spinal neuroblastoma developing into a neurocytoma :* Fresh-wet film of biopsy-specimen, excised, at level of second lumbar nerve-root, from the cord of a man aged forty-five years. The presence of these aberrant nerve-cells, some of them of large size and possessing more than one nucleus, enabled a diagnosis of the nature of the tumour to be given during the operation. *Lower left inset* (× 400) shows, from another part of the film, an unusually large neoplastic nerve-cell with two nuclei, indicated in the *upper right inset* (× 100) by an arrow. (W.E.H. case.) Fresh-wet preparation in toluidin blue. × 400.

a few small chromatin-granules). In the cytoplasm, Nissl- (" tigroid ") bodies are usually scanty, and any neurofibrils found are situated mostly in the cell-processes rather than in the cell-body. One of these processes can generally be distinguished as the axon, which is usually non-medullated. Supporting glial cells (including perineuronal capsular and Schwann-cells), blood-vessels with a varying amount of collagenous connective tissue round them and also as a rule forming a general enclosing capsule, complete the structure of these tumours. Degenerative changes of the usual types are common in these neoplastic nerve-cells, including invasion of them by phagocytic " satellite-cells "—*e.g.*, of the capsules, if they are cells in a ganglion [1]—microglia, etc., a process known as " neuronophagia " or " neuronophagy " (pp. 1014 and 1192).

(For the varieties of tumour which originate from the suprarenal medulla and the allied paraganglia—the neuroblastomas of young children: the neurocytomas (" ganglioneuromas ") of both children and adults: and the " paragangliomas " or " phæochromocytomas " containing chromaffin cells, *see* pp. 845–7.)

(9) **Ependymomas** and **Ependymoblastomas** are respectively the simpler and the more primitive varieties of tumour which arise from the lining-cells of the ventricular system, especially of the fourth ventricle, and from the central canal of the spinal cord. Both varieties are usually slow-growing and benign in character. In sections of general neurological material, little groups of misplaced ependymal cells in the subependymal tissues of the ventricles and also around the central canal of the cord are of common occurrence, and may be suspected as the potential starting-points of these tumours. **Proliferations of ependyma,** patchy or diffuse (Figs. 707–8), also occur as part of certain

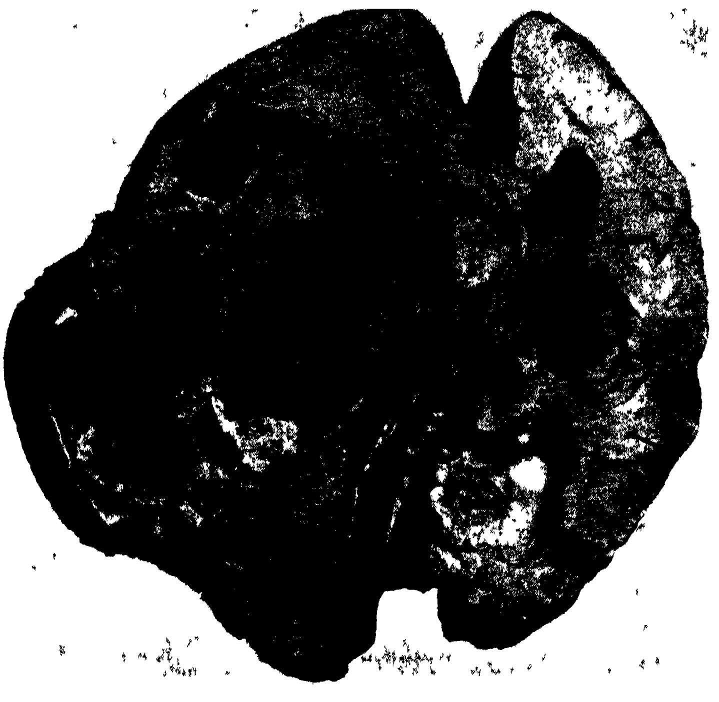

FIG. 705. *Ependymoblastoma* in a girl of seven years, with an eighteen months' history. The tumour occupied the greater part of the left cerebral hemisphere and contained several cystic cavities. The bulge on the left is a hernia following a decompression operation. (*Cf.* Fig. 688.)

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[1] For analogous " neuronophagy " of nerve-cells in ganglia by capsular cells, though *not* in relation to tumour-formation, *see* Figs. 766 to 768, pp. 1194 to 1197.

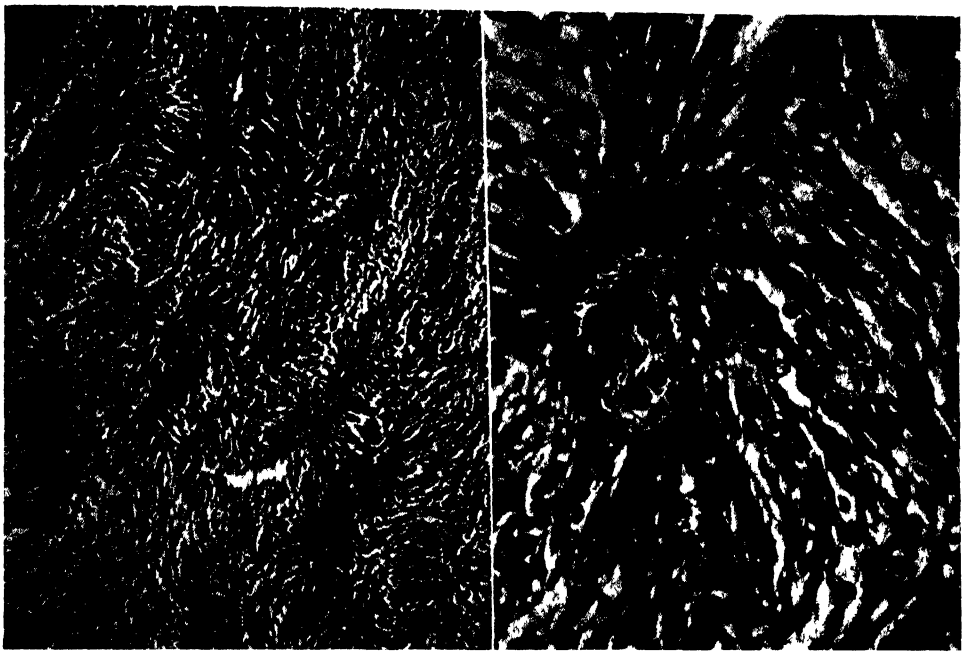


FIG. 706. *Ependymoblastoma*: Low- and high-power views of section of the tumour illustrated in Fig. 705 showing the elongated cells suggestive of ependymal spongioblasts radiating around small vascular channels, to the outer aspect of which they are attached by stout processes. The differential diagnosis here between ependymoblastoma (or ependymoma), polar spongioblastoma and astroblastoma was a problem of considerable difficulty. Hæmatoxylin and eosin. × 75 and 300 respectively.

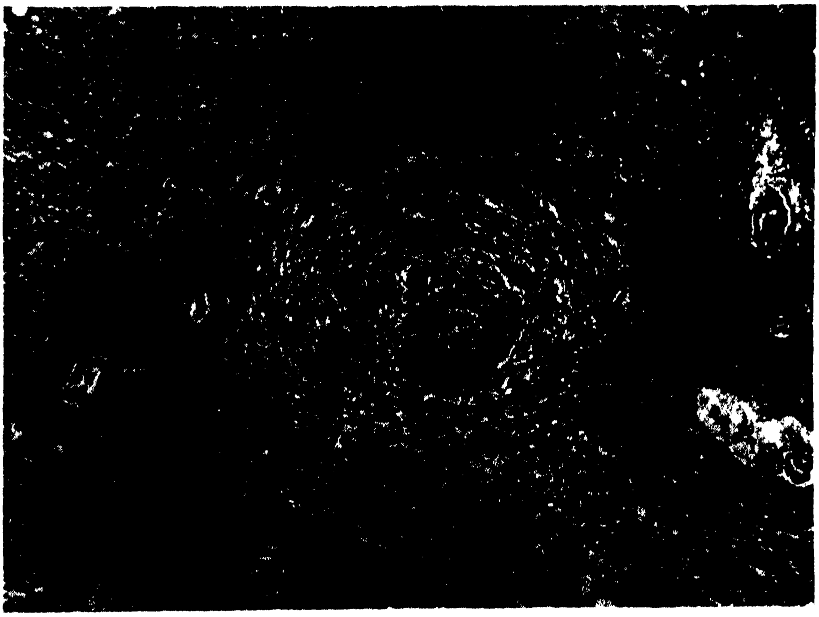


FIG. 707. "*Ependymomatosis.*" *Ependymal proliferation* in the thoracic region of the cord in a case of multiple neurofibromatosis in a male age twenty-five years, showing early proliferation and outward spread of the central ependymal cells. Note also the peri-central gliosis. Syringomyelic cavities were present at other levels in this cord, and a very early stage in the formation of these is seen at the right-hand margin of this illustration (*see* p. 1163 *et seq.*). Hæmatoxylin and eosin. × 100.

"multiple-tumour syndromes," *e.g.*, tuberous sclerosis (p. 1134) and central neurofibromatosis (p. 1135), being then probably "congenital" in origin and, if not taking the form of definite localised tumours, may conveniently be described as an "**ependymomatosis.**" When small irregular and sometimes wart-like projections are present on the surface of the ventricular lining, probably as the result of some chronic irritative process, the condition has been termed "**granular ependymitis,**" in which, however, proliferation of the sub-ependymal glial tissue may often be a more marked phenomenon than that of the lining ependymal cells themselves.

As already noted, tumours of this sub-group, composed of or derived from ependymal spongioblasts, show analogies and resemblances on the one hand to neuro-epitheliomas and on the other to astroblastomas. The cells often possess well-marked vascular processes, arranged radially round the blood-vessels, producing the appearance of pseudo-rosettes. Although the cilia present in early life may have largely disappeared from the normal ependymal lining-cells of the ventricular system, cystic tumours still showing them may occur, *e.g.*, in connection with the third ventricle or in the spinal cord ; and even where the cilia themselves are absent, the little basal granules or **blepharoplasts** associated with them (but in the cells of these tumours situated, not near the surface, but *deeply* in the cytoplasm) usually persist and are demonstrable by special methods.

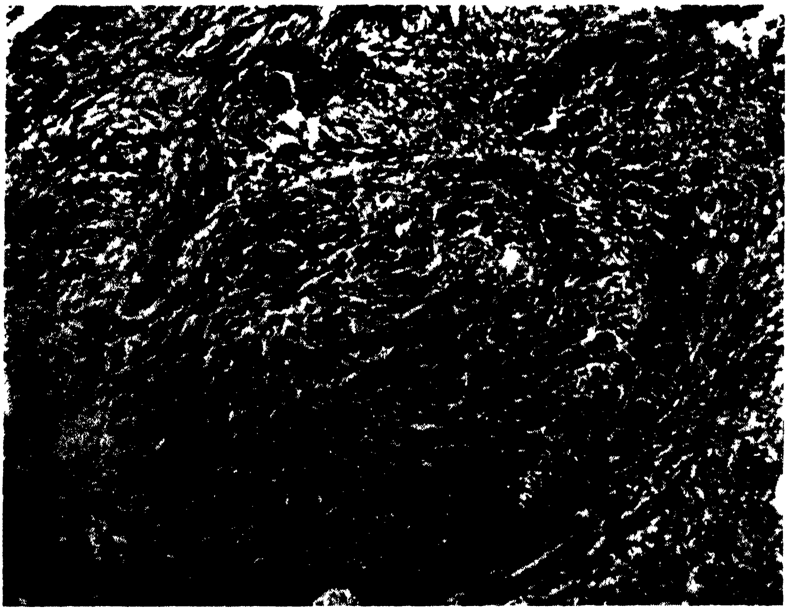


FIG. 708. "*Ependymomatosis*" in thoracic region of spinal cord : *ependymal proliferation* and *peri-central gliosis* : a further stage in the process, from the same case as Fig. 707. Hæmatoxylin and eosin. × 100.

(10) **Pinealomas** (p. 848). The characteristic tumours growing from the epiphysis cerebri contain **two types of cells** in groups (1) loose masses of **larger** spherical cells with large spherical or ovoid nuclei and abundant finely-granular cytoplasm, corresponding to the parenchymatous cells of the pineal body, some of them possessing fine processes with curious bulb-like endings : and (2) **smaller** lymphocyte-like cells lying in groups amongst a varying amount of connective-tissue stroma. When of more primitive and rapidly-growing type, they are analogous to the glial variety of medulloblastoma and may then be designated **malignant pinealomas** (or pineoblastomas). Tumours of the pineal region are of importance because of the pressure they may exert upon neighbouring structures, *e.g.*, the splenium of the corpus callosum and the great cerebral vein of Galen above : the tectum of the mid-brain (the quadrigeminal plate) and aqueduct (compression of this causing hydrocephalus) : and the brain-stem below and the cerebellum behind it. The third ventricle may become filled with the tumour, leading to compression of the optic

thalami on either side of it and of the hypothalamus, infundibulum and pituitary farther forwards. In addition to results common to cases of intracranial tumour in general, paralysis of upward conjugate deviation of the eyes, *i e.*, inability to look upwards, together with failure of vision and other eye-symptoms, and bilateral partial deafness from involvement of the medial geniculate bodies are amongst the few distinctive symptoms of tumours in this region. Compression of the pituitary and of the hypothalamus from

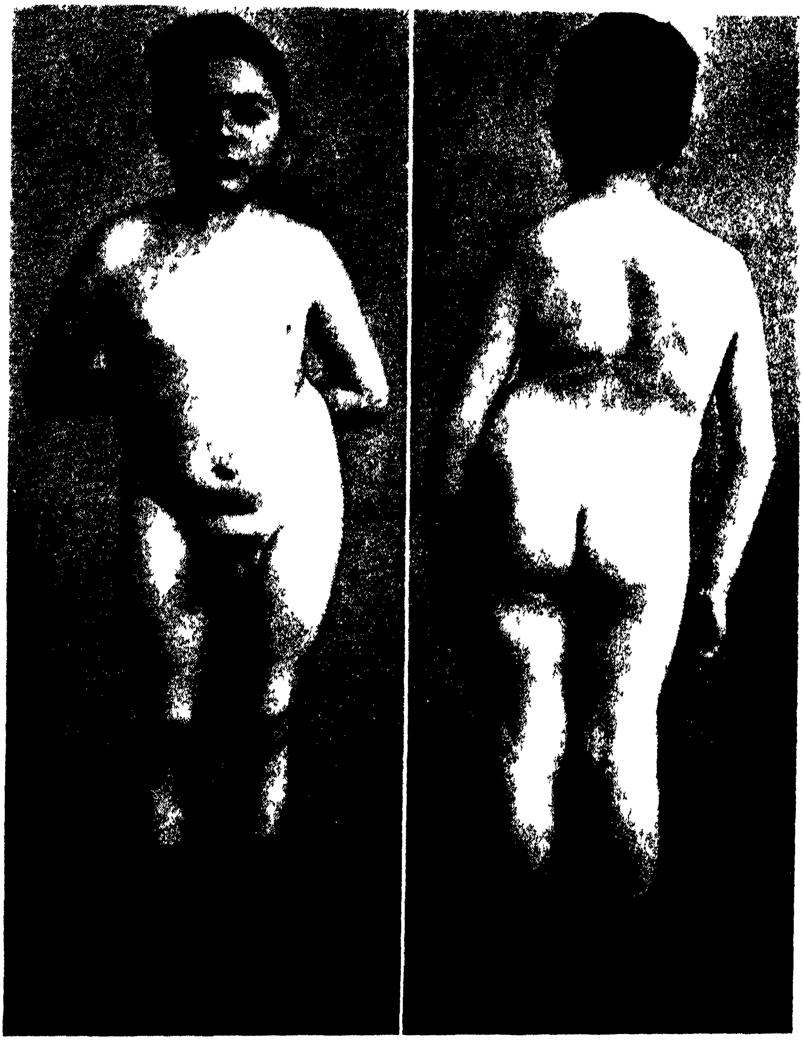


FIG. 709 *Hypopituitarism, combined with the pineal syndrome of precocious puberty,* in a boy aged sixteen at the date of the photograph, but in whom the clinical picture was established well before the usual time of the development of puberty (Dr Worster Drought's case, W E H)

above, by the mechanism just outlined may produce a clinical combination of the syndromes of both pineal and pituitary tumours

For a description of **pineal teratomatous** and other forms of tumour both cystic and solid (pineal "dermoids," "cholesteatomas," etc.), growing from the "pineal anlage," see pp. 351, 848 and *cf* 1098. Some of these pineal teratomatous tumours, when occurring in boys before puberty, are associated with the striking clinical picture of **macrogenitosomia** or **pubertas præcox** (precocious puberty), in which there is precocity both of mental and bodily development, the latter especially of the genitalia and secondary sex characters (hirsuties and precocious changes in the skeleton, larynx, etc.). Every male child suffering from such a pineal tumour does not necessarily exhibit this syndrome, but when present it is found practically only in male children. When adiposity is also present in patients with pineal tumour, it is probably not the result of the presence of the tumour of the epiphysis itself, but of pressure upon the hypothalamus and pituitary, either directly by the growth, or sometimes brought about indirectly by hydrocephalic distension of the third ventricle and infundibulum.

The occurrence of **corpora arenacea** or calcareous particles (see below) in the pineal body from adolescence onwards is so common that it may be regarded as a normal phenomenon and their opacity to X-rays often affords a useful landmark in radiograms of the head.

Tumours of the Choroid Plexus. The choroidal epithelium, although of parallel development with the ependymal cells lining the ventricles, originates more directly from the embryonic medullary tube and its cells; and the cells of tumours derived from them do *not* possess cilia or their accompanying blepharoplasts. **Papillomatous tumours** of the choroids are practically invariably **simple** or benign in character, and occur mostly in childhood (Figs. 710 and 711). "Malignant papillomas" have not infrequently been described, but many of these have undoubtedly been secondary papillomatous growths originating from some unsuspected primary malignant tumour elsewhere, most commonly a **bronchial carcinoma** (Figs. 349 (A) and (B), p. 570: Fig. 351, p. 573: and Figs. 733–5, pp. 1146–7), metastatic cells from which when spread by the blood-stream being liable to become lodged in vascular structures such as the choroid plexuses.

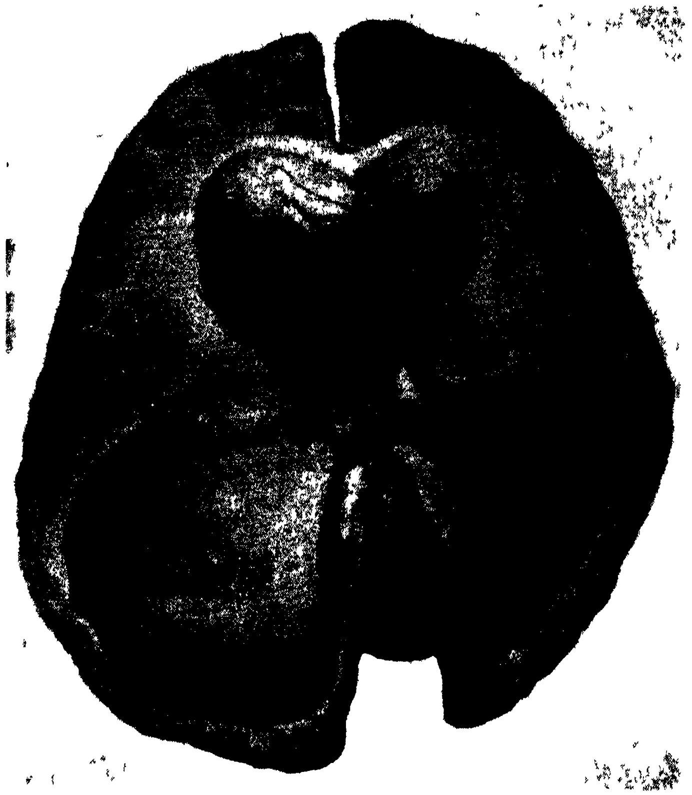
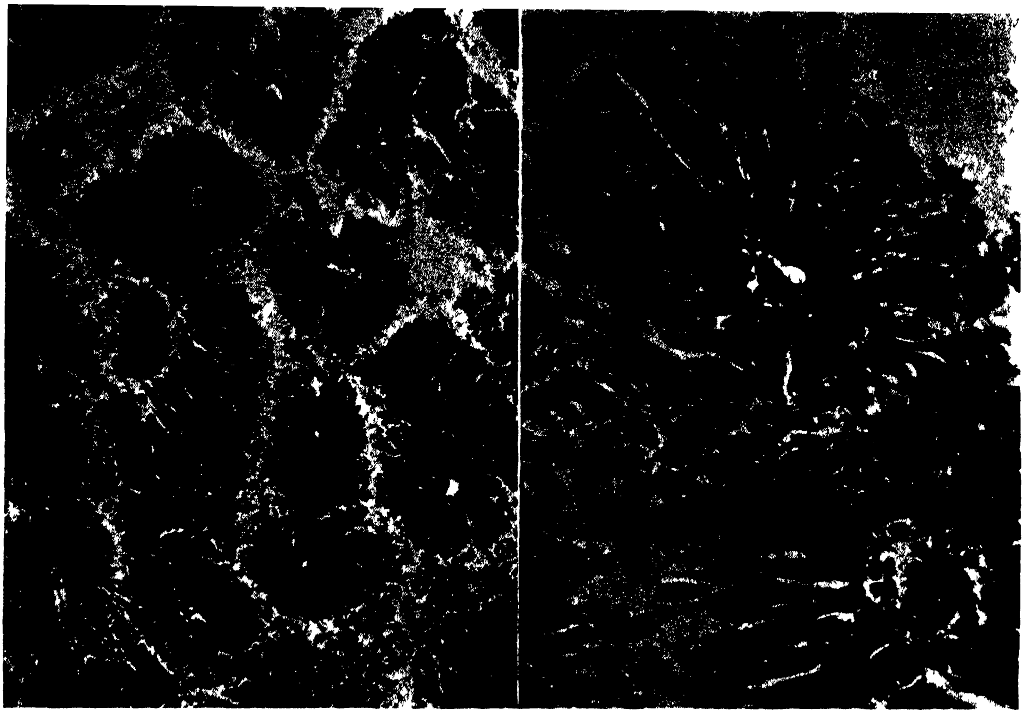


FIG. 710. *Choroidal papilloma* in a boy aged ten years. This congenital tumour gave rise to pronounced hydrocephalus, but produced comparatively little mental deterioration, the case, before being sent to hospital, having been regarded merely as one of "juvenile delinquency." (Dr. Colin Edwards' patient, W.E H.)

The so-called "**brain-sand**" or calcified particles, **corpora arenacea,** of such frequent



(A) × 100 (B) × 350

Fig 711 *Choroidal papilloma* low and high power views of sections from the tumour illustrated in Fig. 710, showing its compound papillomatous structure and the high columnar tadpole shaped epithelial cells arranged radially round scanty vascular connective tissue cores Contrast the appearances of this tumour which gives *no* micro chemical reaction for mucin with those seen in secondary bronchial carcinomatous growths (*e g*, in Figs 351 (*d*), p 573, and Fig 354 (A,), p 575) which may *simulate* choroidal tumours Masson s trichrome stain

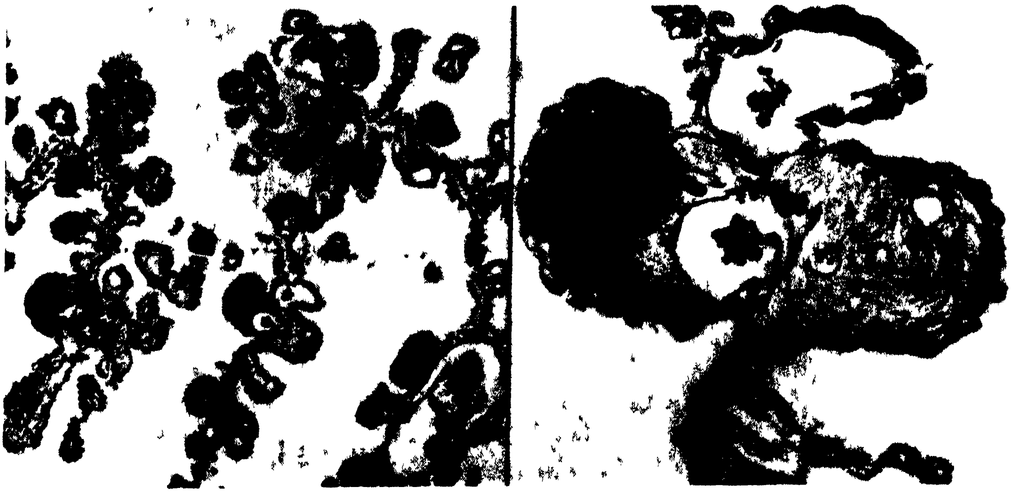


Fig. 712 *Corpora arenacea or calcified particles in the degenerated choroid plexus* of a man aged fifty-four, who died of cerebral tumour which had caused dilatation of the ventricles. Hæmatoxylin and van Gieson's stain. × 85 and 350.

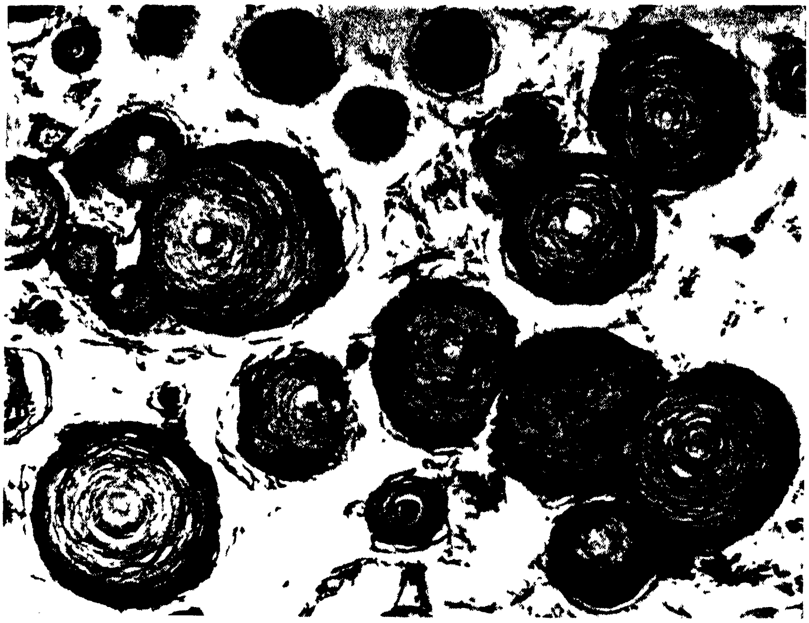


FIG. 713. *Corpora arenacea in choroid plexus* of a boy aged seventeen years, with *multiple neurofibromatosis*, showing concentric structure around small central vessels, obliterated in a few of the spherules. (*Cf.* Fig. 714 from same case.) Mallory's connective-tissue stain × 85.

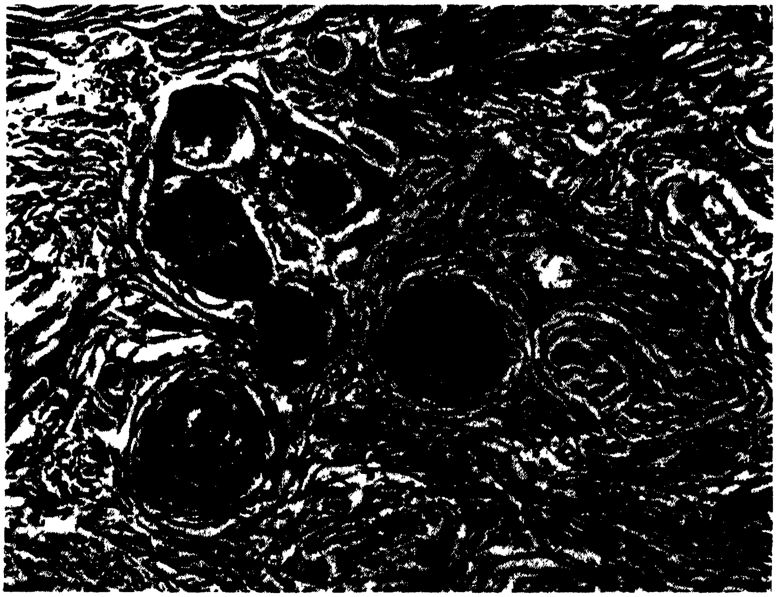


FIG. 714. *Corpora arenacea in a left cerebello-pontine-angle tumour* in a case of ***multiple neurofibromatosis*** in a boy aged seventeen years, from which Fig. 713 is also taken. Note the "psammomatous" formation, and compare with other examples of corpora arenacea, degenerative and psammomatous, illustrated in Figs. 671 and 674 on pp. 1091 and 1093. Hæmatoxylin and eosin. × 100.

occurrence in the choroid plexuses (and also in the pineal body, p. 1122), are, in these situations, practically always degenerative and *not* neoplastic in their nature and origin.[1] These corpora arenacea are due to calcification supervening in patchy areas of degenerative thickening in the walls of the choroidal vessels themselves and in the delicate perivascular connective tissue lying between these vessels and the surface choroidal epithelium (Fig. 586, A, p. 971). They are very common, not only in old age but in middle life, and may be found even in childhood ; and may be exaggerated in certain diseases, for example in multiple neurofibromatosis (Fig. 713, and *cf.* p. 1135 *et seq.*). Hypertrophy, or perhaps more accurately **hyperplasia,** of the choroids is common in many cases of hydrocephalus, though in the congenital variety of that condition there may be various degrees of partial non-development, degenerative thickening or atrophy (pp. 968 70, and Fig. 586, p. 971).

Investigation of the Glioma-Group of Tumours by methods of Cell-Culture. We are indebted to Drs. Dorothy Russell and J. O. W. Bland, of the London Hospital, for the accompanying beautiful illustrations of their careful and suggestive work on this subject [2] (Figs. 715–17). They have been successful in obtaining living cultures from biopsy-specimens of most varieties of gliomatous tumours (an exception being the ependymomas), and they conclude that the *glioma-group* possesses certain characteristics *in common*, for example, the early development round the explant-colony of a delicate projecting fringe of cell-processes, followed by the migration outwards into the surrounding medium of elongated bipolar cells, often tending to form end-to-end chains, along the sides of which other cells emigrate to reach the end of the chain and there take up their position--a phenomenon noted especially in the cell-cultures from Percival Bailey's polar glioblastoma or spongioblastoma (a tumour which they regard as closely allied to the astrocytomas (*cf.* p. 1108). While emigrating, the cells are mobile and plastic ; but, after they have emigrated, they tend to settle down and the cells of each variety of tumour maintain their individuality, for example, when they come to rest, polar cells resume their spindle-shape, and astrocytes resume their triangular or stellate outlines. They may form networks, sometimes in association with fibroblasts, towards which they often show distinct orientation—for example, spindle-shaped cells may become united to the fibroblasts by the tips of their polar processes. In most of the cultures, the phenomena were those of **migration** and **alteration in shape,** and then **degeneration.** True growth, *i.e.*, multiplication of the tumour-cells by mitotic division, was observed only in three instances (one polar-spongioblastoma and two glioblastoma-multiforme specimens) out of the twenty-two tumours investigated. In none of them did these investigators find any evidence of amitotic division. Our readers will find much of interest in these illustrations, and for further details should consult the original papers.

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[1] Hence in this connection it is well to discard the misleading term " psammoma " for such *non*-neoplastic lesions and to reserve it for the " psammomatous " members of the meningioma group of tumours described on p. 1088 *et seq.*

[2] " A Study of Gliomas by Methods of Tissue Culture," *Jour. Path. and Bact.*, 1936, **36,** 271 : " Further Notes on the Tissue Culture of Gliomas with special reference to Bailey's Spongioblastoma," *ibid.*, 1934, **39,** 375 : and (with the late Dr. R. G. Canti) " Tissue Culture of Gliomata," *Proceedings of the Association for Research in Nervous and Mental Disease*," 1935, **16,** 1.

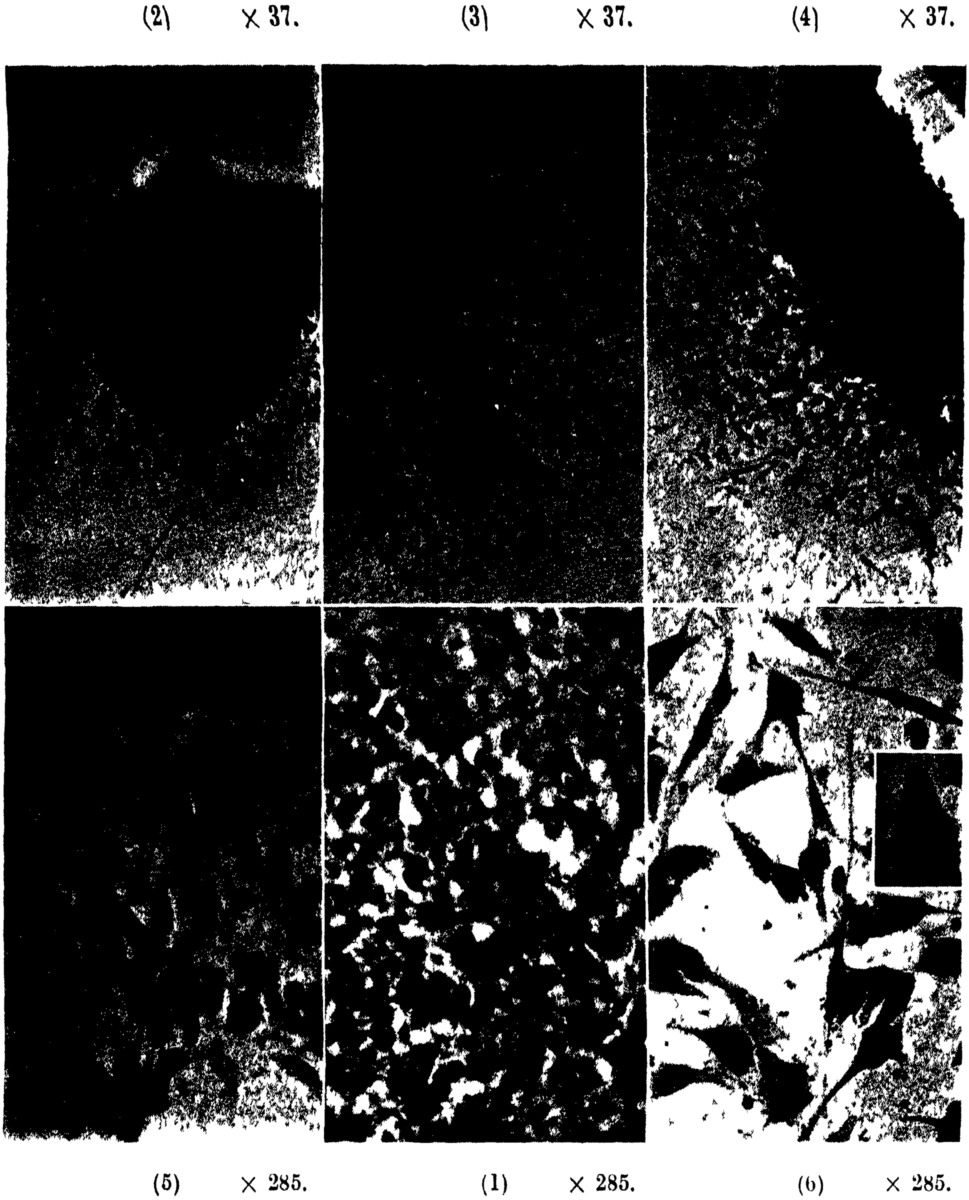


FIG. 715. *Glioblastoma multiforme. Cell-cultures.* (By courtesy of Drs Dorothy S. Russell and J. O. W. Bland.)

(1) Paraffin-section of one of the original tumours (hæmatoxylin and eosin).

(2) Forty-eight-hours' culture in human serum (sudan III and hæmatoxylin).

(3) Four-day culture in fluid medium (Delafield's hæmatoxylin and erythrosin).

(4) Twelve-day culture in fluid medium (Mallory's phosphotungstic acid-hæmatoxylin).

(5) and (6) Tumour-cells in migration-zones of (2) and (4) respectively, showing various shapes of cell, including both spindle-shaped and stellate forms. Inset in (6): a large multinucleated cell resembling the giant-cells often present in these tumours (Mallory's phosphotungstic acid-hæmatoxylin).

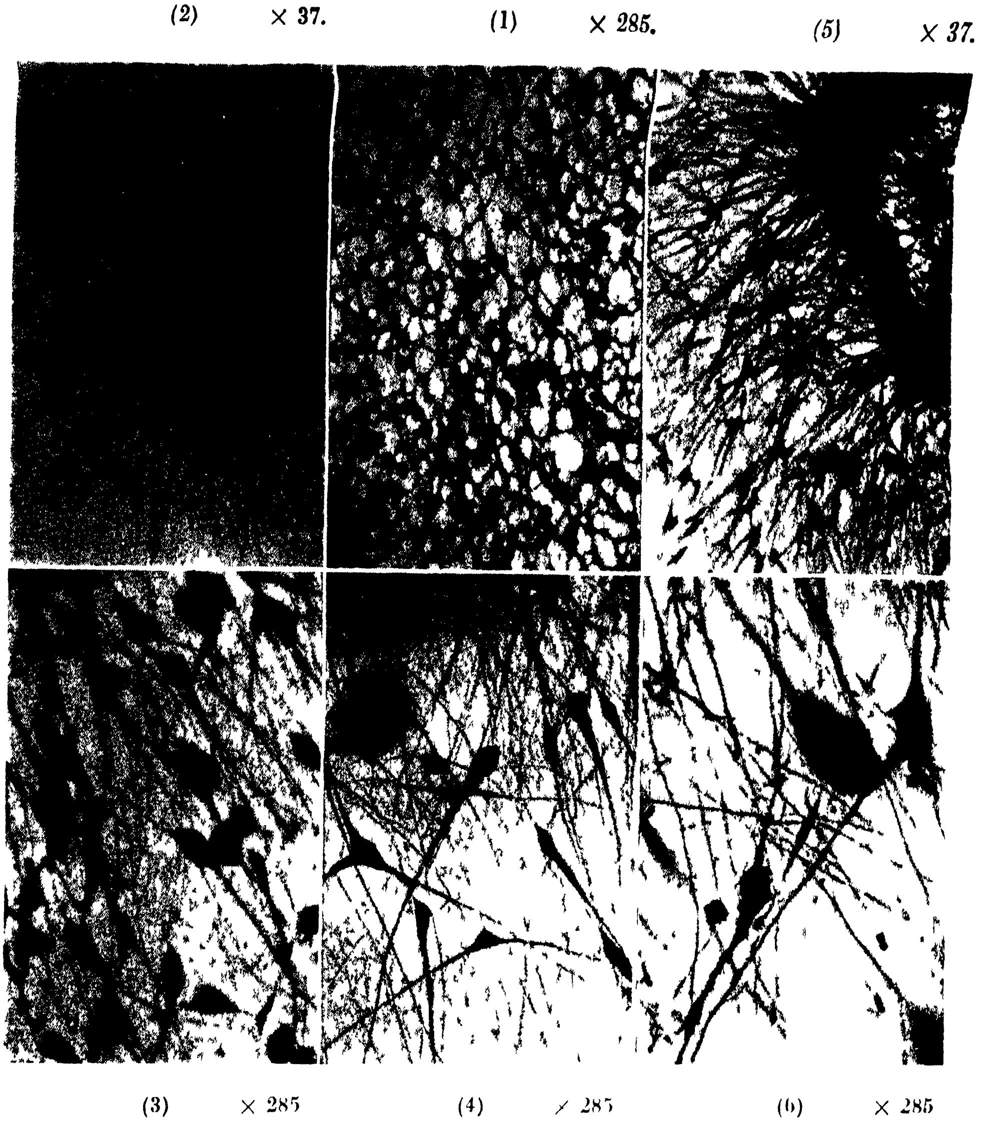
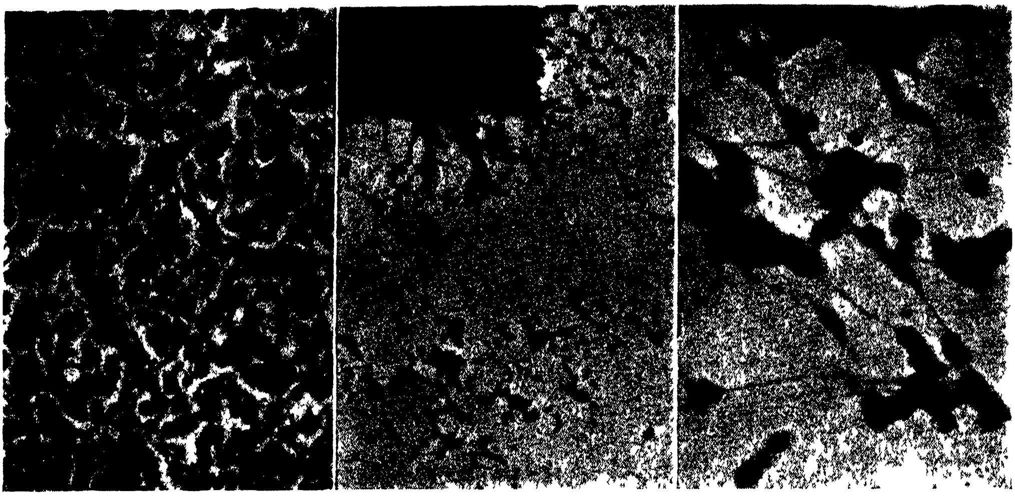


Fig 716 *Astrocytoma Cell cultures* (By courtesy of Drs Dorothy S Russell and J O W Bland)

(1) Paraffin section of one of the original tumours (hæmatoxylin and eosin)
(2) Cell culture at five days, showing radiating zone of migrating astrocytes
(3) Zone of migration round the colony shown in (2), with formation of abundant glial fibrils
(4) Zone of migration in an eight day culture from tumour, section of which is shown in (1)
(5) Cell culture, from another astrocytoma, at eleven days
(6) Astrocytes and glial fibrils in zone of migration of (5)
(All the cultures were made in fluid media, and the films are stained with Mallory's phosphotungstic acid hæmatoxylin)



(1) × 285. (2) × 37. (3) × 285.

FIG. 717. *Oligodendroglioma : Cell-cultures.* (By courtesy of Drs. Dorothy S. Russell and J. O. W. Bland.)

(1) Paraffin-section of original tumour (hæmatoxylin and eosin) (*cf.* Fig. 699, p. 1114, and description in text, pp. 1113–4).

(2) Five-day culture in fluid medium, showing clumping of the migrated tumour-cells remote from the explant (phosphotungstic acid-hæmatoxylin).

(3) The same showing migrating cells, mostly spindle-shaped with scanty cytoplasm and at each end a long slender process in which there are no glial fibrils. Where they have come to rest, they become arranged in clumps of spherical, pear-shaped, or polygonal cells (phosphotungstic acid-hæmatoxylin).

The Experimental Production of Intracranial Tumours

Seligman and Shear,[1] of Harvard, describe the successful artificial induction of tumours in mice by planting pellets composed of a form of methylcholanthrene (p. 282 *et passim*) in the cerebral cortex. Out of twenty young male mice employed in the experiment, a tumour which invaded the bones of the skull was produced in four : a fibrosarcoma of the meninges in two : and in seven some form of glioma, varying histologically from an astrocytoma to a locally-malignant glioblastoma multiforme. These tumours were thus produced by the process of the **induction of anaplasia** in previously fully-differentiated glia-cells : and *not* by the stimulation of pre-existing embryonic " rests " or " residues " to proliferate. These authors have also succeeded in transplanting two of these artificially-induced experimental tumours, one of them a glioma, through several generations of fresh mice.

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[1] " Studies in Carcinogenesis : VIII. Experimental Production of Brain Tumours in Mice with Methylcholanthrene," by A. M. Seligman and M. J. Shear, Harvard. *Amer. Jour. Cancer,* 1939, 37, 364.

TUMOURS AND MALFORMATIONS OF THE BLOOD-VESSELS OF THE CENTRAL NERVOUS SYSTEM

Excluding non-neoplastic conditions such as subdural hæmatomas and aneurysms, considered respectively on pp. 974–7 and 1042–6, we adopt here the convenient subdivision of these vascular lesions into (1) "**angiomatous malformations**" and (2) "**hæmangioblastomas**" or true neoplasms of blood-vessel elements, suggested by Cushing and Bailey.[1]

(1) **Angiomatous Malformations.** Opinion differs as to whether the **vascular malformations** are of the nature of **developmental anomalies** rather than true neoplasms, but, although they may still be capable of undergoing subsequent alterations in size and character and are not comparable to the angioblastomas or true vascular tumours, they may conveniently be considered at this point.

These **anomalies of the cerebral and other vessels** may, according to the size, distribution and nature of the vascular unit involved, take the form of :—

(*a*) The rare **telangiectases,** mainly of **capillaries,** analogous to telangiectases occurring in the skin. They are found in the upper part of the pons (Cushing and Bailey) and in the floor of the fourth ventricle (Virchow).

(*b*) **Venous angiomas** of the nature of dilatations or **varices** are found on the surface or embedded, sometimes deeply, in the sulci of the brain,[2] and may occur also along the spinal cord.

(*c*) **Arterial** or **arterio-venous angiomas,** situated mainly in the area of cortical distribution of the middle, and less frequently of the posterior, cerebral arteries. These various anomalies often remain symptomless during life and are discovered only fortuitously at autopsy ; or in some cases, especially if involving some part of the motor cortex, they may produce attacks of Jacksonian epilepsy. They are sometimes associated with the presence of a congenital " port-wine " **nævus** of the **face** and vascular changes in the eye (buphthalmos) on the **same** side as that of the cerebral lesion (" Sturge-Weber disease "—*see* p. 1134). For the diagnosis of some of these vascular lesions, radiography may be employed after injection of a radio-opaque substance into the carotid artery of the same side in carefully chosen cases (first footnote, p. 1042). These arterial angiomas originate from the pial vessels and usually have dilated arterio-venous communications (the "*hæmangioma racemosum arteriole et venosum*" of Schley). They are thus composed of sinuous arteries passing into the corresponding veins, and, in the vivid words of Cushing and Bailey,[3] they form, when seen at operation during life, " an actively pulsating snarl of vessels " very unlike the much less striking post-mortem appearances of such a lesion.

Histologically, an important point emphasised by Cushing and Bailey is that traces of nervous tissues, *e.g.*, glia, can be found as a " background " between the vascular channels of these angiomatous anomalies of the cerebral vessels.

(2) **The Hæmangioblastomas** (p. 332) or true vascular tumours composed of angioblastic elements are found almost exclusively **in the cerebellum** as their site of election and where they tend to give rise to **cystic formations** (*see under* Lindau's disease, p. 1131), though in some instances the lesions may be, and

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[1] " Tumours Arising from the Blood-vessels of the Brain," Baillière, Tindall & Cox, London, 1928. The writings of Lindau (*see* footnote on p. 1131), and of Hilding Bergstrand of Stockholm and his collaborators (" Gefässmissbildungen und Gefässgeschwülste des Gehirns," 1936, Leipzig) should also be consulted by those interested.

[2] " Venous Angioma of the Cerebrum " (with coloured illustrations), by Worster-Drought and Carnegie Dickson, *Jour. Neurol. and Psychopath.*, 1927, **8**, 19.

[3] *Loc. cit.*, p. 35.

may remain, solid (Fig. 718). They appear to arise from some primitive "vascular anlage" such as the "area postrema" of the fourth ventricle. Rare instances in the spinal cord (*cf.* pp. 1132–4) and in the retina have been recorded, but the cerebral hemispheres seem to be practically exempt from the occurrence of true hæmangioblastomas. As noted under Lindau's disease (p. 1132), they may be predominantly capillary, cellular, or cavernous, but usually show varying admixtures of these types. Microscopically, the presence of a network of reticulin is characteristic.

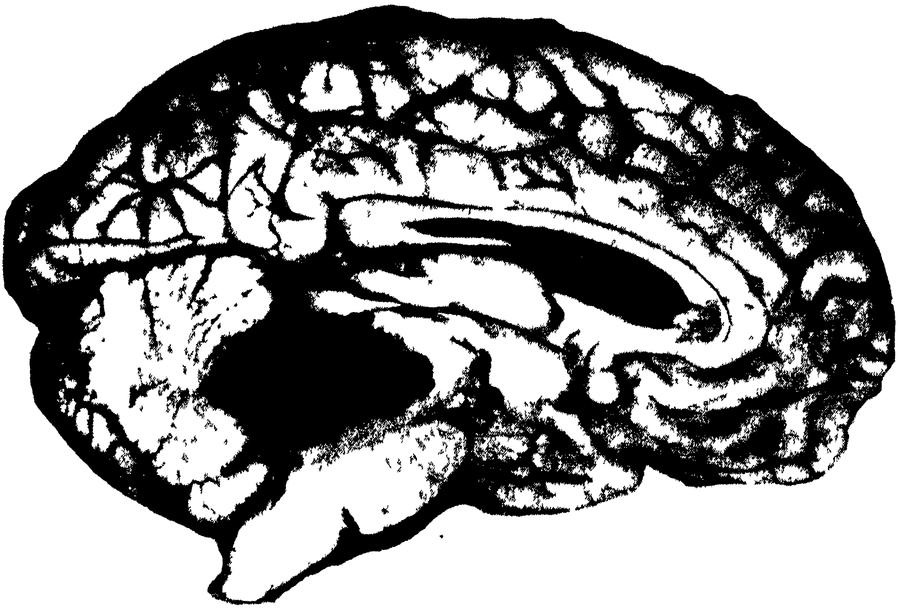

FIG. 718. *Cavernous angioma arising from the floor of the fourth ventricle* in a female aged twenty five years. The bristles have been introduced into the aqueduct, which is still patent There is moderate distension of the third and lateral ventricles. (W.E H. case.)

MULTIPLE NEOPLASTIC SYNDROMES[1] affecting the nervous system, including the so-called **Neuro-Ectodermal Dysplasias,** constitute an interesting group of developmental abnormalities, usually congenital and often heredo-familial which, though rare, are of importance because of the information which a study of their nature and incidence affords on the problems of the causation of congenital abnormalities in general and of tumour-formation in particular. The nervous system and cutaneous structures, both of them ectodermal in origin, are the sites of election of the lesions found particularly in two of the more important of these syndromes, **tuberous sclerosis** and **multiple neurofibromatosis,** and the lesions themselves are very varied and are generally classed as "tumours." The manifestations of such syndromes are, however, not necessarily confined to ectodermal structures ; several, and sometimes many, tissues and organs are the seat of these tumour-like growths and developmental abnormalities. Thus, in the "**angiomatoses**" of the central nervous system, retina and skin—for example, the syndromes known as **Lindau's, von Hippel's** and **Sturge-Weber's diseases** (*see below* and p. 1134) —the mesoderm-derived vascular tissues in particular are involved; whilst in **tuberous sclerosis** (p. 1134), in addition to the ectodermic central nervous system and skin, the heart, kidneys, liver and other organs may be affected.

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[1] *See* second footnote on p. 1069.

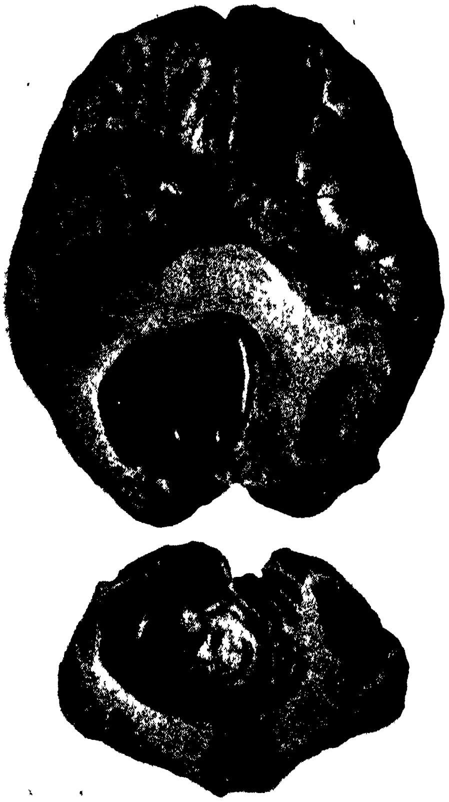

FIG. 719. *Lindau's syndrome: large cerebellar cyst with characteristic cavernous hæmangiomatous mural nodule in its posterior wall*, from a female aged thirty-five years. The cyst contained highly albuminous yellowish serous fluid (shown still retained in position in the upper section). (W.E.H. case.)

LINDAU'S DISEASE (Syndrome of von Hippel and Lindau). This rare syndrome was defined by Arvid Lindau[1] (of Lund, Sweden), as "a systemic disorder with **angiomas** of the **hind-brain** and the **retina,** with co-ordinated **malformations** or **tumours** of the **pancreas** or the **kidneys.**" Amongst his cases he found a positive family history in 20 per cent. The usual site of the vascular tumour, called by Cushing and Bailey a "hæmangioblastoma," is the cerebellum, much more rarely the medulla oblongata or spinal cord. The tumour itself is composed of proliferated blood-vessels and is sometimes quite small, perhaps not larger than a pea ; but it tends to give rise to cyst-formation in its immediate neighbourhood. The resulting "**cerebellar cyst**" may gradually increase in size and produce serious symptoms, although the capillary or other form of angioma itself in most instances remains small and embedded in, or projecting from, the wall as the so-called "**mural nodule**" (Fig. 719). The nodule itself is evidently a congenital abnormality, but the symptoms due to cyst-formation may not supervene until the third or fourth decade of life ; and it is interesting to note that, in cases in which such a cyst is in process of formation and enlargement, there is often the history of some preceding trauma which may have acted as the immediate or exciting cause of the leakage leading to the production of the cyst. Lindau describes the vessels or vascular spaces of the nodule as separated from each other by an abundant intervascular tissue containing numerous swollen phagocytic fat-laden endothelial cells (" pseudo-xanthomatous " or " foam-cells "—to the presence of which as a secondary phenomenon in tumours we have drawn attention on pp. 1084–5 (Figs. 659–60) : *cf.* under " Xanthosarcoma," p. 1228) which sometimes obscure the original vascular nature of the growth. Histologically these hæmangioblastic nodules may be subdivided into those which are predominantly **capillary, cellular,** or **cavernous** respectively ; but varying admixtures of these constituent elements occur in individual tumours. All show a characteristic reticulin-network, which is well demonstrated by Perdrau's silver-carbonate impregnation-method. Lindau states that the formation of the cyst is due to the " highly exudative power in these hæmangioblastomata," and the consequent transudation of blood-plasma, a process which, as just mentioned, may perhaps be initiated by trauma. Excision of this mural nodule prevents the refilling of the cavity and cures the condition, whereas otherwise, after simple evacuation of the highly albuminous plasma-like fluid, it merely re-accumulates. The wall of the cyst consists of compressed glia with no ependymal lining, and the fluid exuded from the tumour collects owing to lack of any appreciable degree of lymphatic drainage in the surrounding brain-tissue. These hæmangiomatous cysts are usually single—rarely bilateral or multiple—and appear in many instances to arise in connection with the " area postrema," a primitive " vascular anlage," described originally by Retzius, at the " posterior " or caudal end of the floor of the fourth ventricle (p. 1130). An analogous cystic formation occurs occasionally in the cerebellum with a small **gliomatous** tumour as the mural nodule (*see* Fig. 696, p. 1111, in which, however, in the case of this particular patient, the glioma is of larger size than in the typical " mural-nodule " type of cyst).

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[1] "Studien über Kleinhirncysten : Bau, Pathogenese und Beziehungen zur Angiomatosis Retinæ," *Acta Pathologica et Microbiologica Scandinavica, Supplementum I,* Lund, 1926 ; and "Vascular Tumours of the Brain and Spinal Cord," Discussion in Sections of Neurology and Ophthalmology, *Proceedings of the Royal Society of Medicine,* London, November 13th, 1930, p. 363. In this Discussion, the "Ocular Hæmangiomatous Formations associated with Vascular Tumours of the Brain and Spinal Cord" were described by E. Treacher Collins (*loc. cit.,* p. 372).

In addition to the characteristic cerebellar cyst, there is, in cases of Lindau's syndrome, not infrequently an **angiomatosis of the retina** (von Hippel's disease), which is therefore important from the point of view of clinical diagnosis ; and there is sometimes also associated **congenital cystic disease** of the **kidneys** or **pancreas,** the latter of which lesions Lindau believes to be almost pathognomonic of this syndrome. Treacher Collins [1] pointed out that : " A retinal angioblastoma is a mesoblastic neoplasm growing in a neuro-epiblastic structure. When the endothelial proliferation exceeds the vascular formation, a hæmangio-endothelioma results. The characteristic appearances of a retinal angioblastoma are due to the retinal arteries being end-arteries. The affection is always progressive, cysts form, hæmorrhages take place, and blindness inevitably results." Cystadenoma of the ovaries, tumours of the suprarenals, anomalies in the vessels of the diploë of the bones of the skull, angiomata and moles (van der Hoeve's " phakomata " [2]), and other rarer abnormalities may also occur as part of this syndrome.

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[1] *Loc. cit.* (*see* footnote, p. 1131) Abstracts of the Opening Papers.

[2] Professor J. Van der Hoeve, of Leiden, Holland, has proposed the general term " phakomatosis " for any syndrome-disease of this type in which " nævi " or " nævoid growths " play a part. The word is derived from φάκος, *phakos*, a lentil, and hence, secondarily, a spot on the body, a mole, or freckle. (" Doyne Memorial Lecture : Eye Symptoms in Phakomatoses," Oxford Ophthalmological Congress, 1932 ; Transactions of the Ophthalmological Society, 1932, **52,** 380–401.)

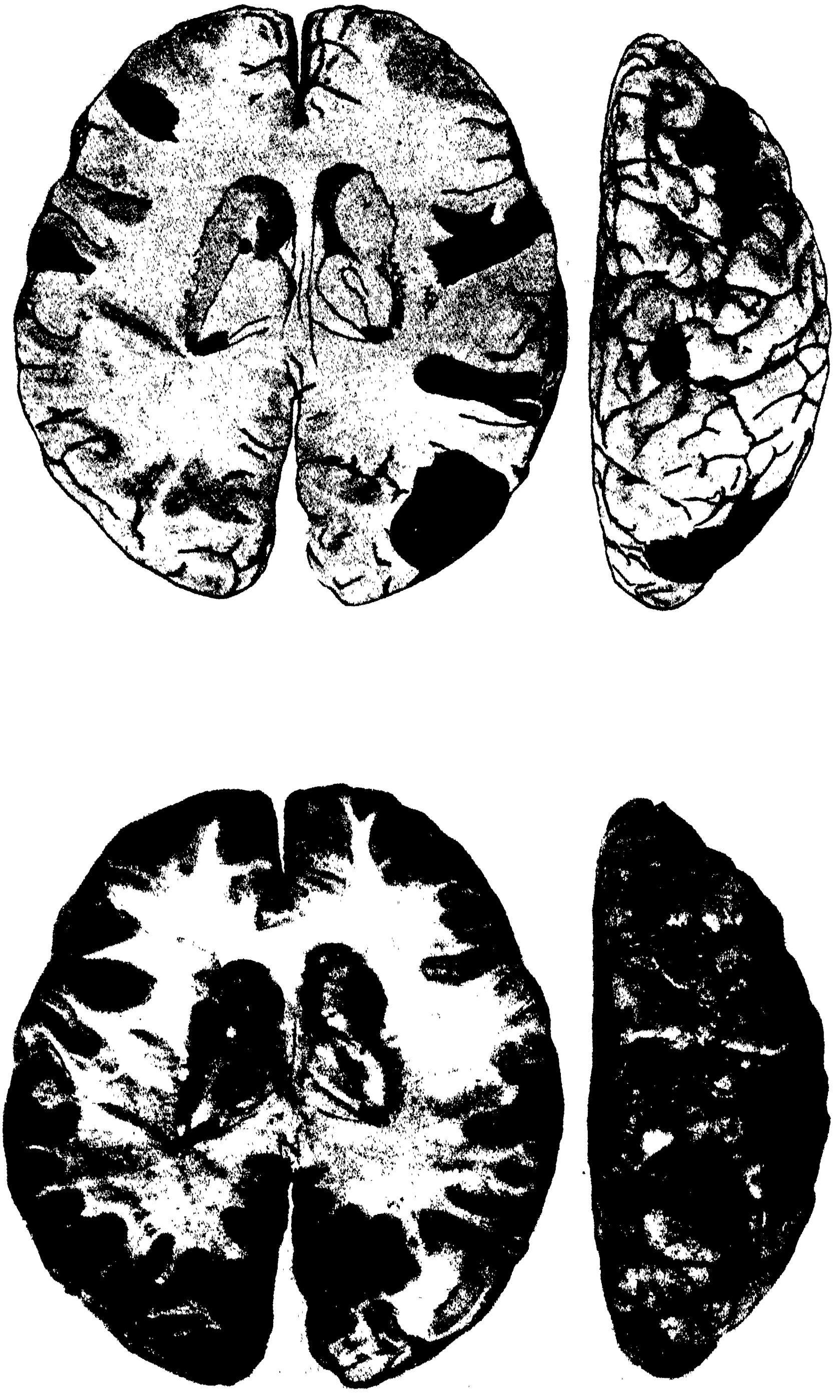

FIG. 720. *Tuberous sclerosis :* surface and horizontal section, showing the tumour-like nodules in the brain. In order to indicate these more clearly, their position is shown in black in the outline-sketch above. Note the small nodules (*see* text, p. 1134) on the walls of the lateral ventricles, as well as the larger " tuberous " masses in both the grey and the white matter towards and at the surface of the hemispheres. (Stewart Fowler and Carnegie Dickson's case, R.H.S.C., Edinburgh.)

Dorothy Russell[1] has reported an interesting example, in a female aged forty-nine, of a capillary hæmangioblastoma in the cervical region of the spinal cord, associated with a syringomyelic cavity extending throughout the cervical and thoracic regions, apparently *not* of the nature of a transudation-cyst.

In relation to Lindau's syndrome and tuberous sclerosis, compare also **Sturge-Weber's disease** (*cf.* p. 1129), in which there is the association of an extensive capillary nævus of the face, usually in the distribution of the trigeminal nerve, and a diffuse leptomeningeal hæmangioma on the surface of the brain on the *same* side as the facial nævus.

TUBEROUS SCLEROSIS[2] (*syn.* **Bourneville's disease,** 1880) is a somewhat rare developmental abnormalty—a multiple congenital-tumour syndrome characterised by the presence of hard, firm, knob-like **nodules in the cerebral cortex** (Fig. 720), some variety of **adenoma sebaceum** (of which " Pringle's nævi " with their " butterfly " distribution on the face are the most characteristic), and, clinically, by **epilepsy** and **mental deficiency** often amounting to imbecility or complete idiocy. The raw-potato-like nodules, scattered sometimes in considerable numbers in the cerebral cortex are, owing to their " cartilaginous " or almost " stony " hardness, more easily felt than seen. They vary in size up to some 15 or 20 mm. in diameter, and are embedded in and replace portions of the convolutions, so that, except for some irregular broadening, the general pattern of these does not show any great distortion (Fig. 720, p. 1133). The surface of the nodules is rather paler than that of the surrounding grey matter, and on section they resemble the white matter in colour, but are composed of a dense feltwork of proliferated glia, often containing " monster " and other unusual forms of glial cells, from which it is sometimes difficult to distinguish certain large and abnormal nerve-cells. Small granular projections, which have been likened to " candle-gutterings," are found on the walls of the ventricles, especially the lateral (Fig. 720) ; and, in a considerable proportion of cases, congenital tumours are present in other organs, for example small glioma-like tumours in the retina (Fig. 695, p. 1110), and rhabdomyomas in the heart-wall or kidney (p. 314). In the skin, in addition to the nodules of adenoma sebaceum there are also occasionally various forms of vascular, pigmented and hairy moles and other developmental abnormalities, including glomus-tumours of the nail-beds (p. 849). Reference is made on p. 1130 to the relationship and analogies between tuberous sclerosis and other multiple-tumour syndromes, particularly neurofibromatosis, and in some of these there may be other associated congenital anomalies, such as defects in the skull and lesions of the vessels of the diploë, spina bifida, single and horseshoe kidney, ectopic testis, etc.

"**Hyperostosis Frontalis Interna.**" For the syndrome associated with this curious " dyscrasia " of the cranial vault and symptoms attributable to disturbance of hypothalamic function, *see* p. 1260 in Appendix at end of book.

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[1] *Journ. Path. and Bact.*, 1932, **35**, 103.

[2] *See* " Tuberous (Tuberose) Sclerosis," by J. Stewart Fowler and W. E. Carnegie Dickson, *Quarterly Journal of Medicine*, 1910, **4**, 43. " Tuber*ous*," meaning " knobbed," *i.e.*, like, or of the consistency of, a *tuber* such as a potato—is a more appropriate form of the English adjective than " tuber*ose*," by which to translate and transliterate Bourneville's term " Sclérose Tubéreuse " ; and is less likely to cause misunderstanding, as the latter word " tuberose " is the English name of *Polianthus tuberosa*, the " common tuberose," a garden-plant belonging to the *Liliaceæ*. We do *not* use the word " Epiloia " as a name for this disease, because, as pointed out by Parkes Weber, its only recommendation is that it does not mean anything !

NEUROFIBROMATOSIS (*see also* p. 301) is a congenital syndrome-disease of which several variants, as well as incomplete forms (French "*formes frustes*," p. 1069), are found. The best known variety of the disease is **peripheral subcutaneous neurofibromatosis,** which, although it had been known for many

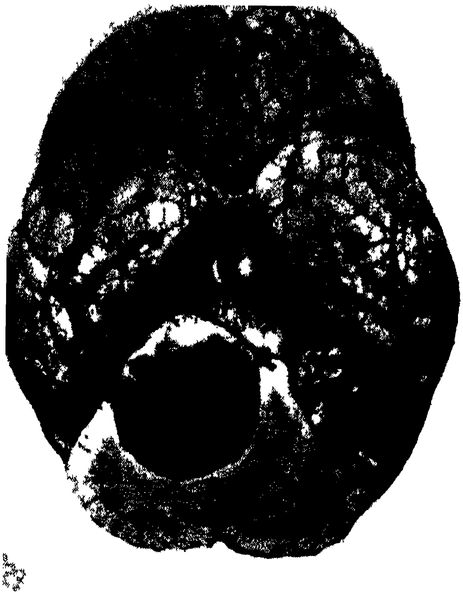

Fig 721 *Central neurofibromatosis or lateral acoustic nerve tumours* in a male aged seventeen years The larger (right hand) tumour, which has undergone extensive degeneration, is cut across horizontally, together with the cerebellum in which it is deeply embedded The smaller (left hand) tumour is uncut Two small tumours are seen on the oculomotor nerves at the centre of the photograph

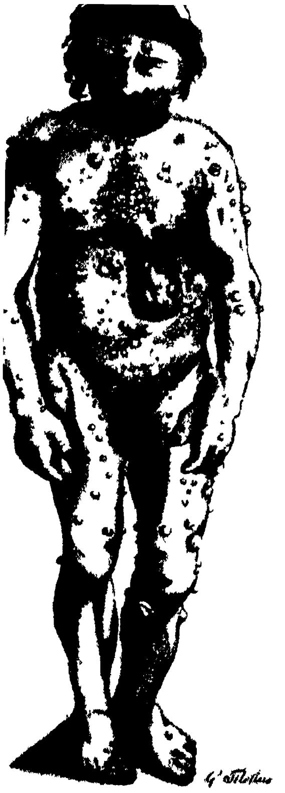

Fig 722. *Peripheral neurofibromatosis* Reduced reproduction of one of the illustrations in the earliest known detailed account of the disease, given by W G Tilesius in his "Historia pathologica singularis cutis turpitudinis," Leipzig, 1793, almost a century before von Recklinghausen's paper was published in 1882

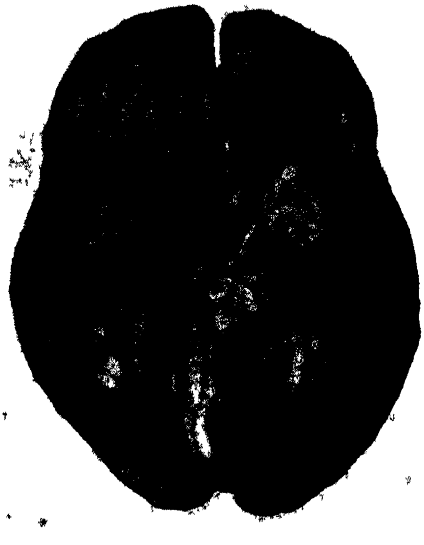

Fig 721a *A unilateral acoustic nerve tumour* at the right cerebello-pontine angle, in a female aged fifty six, in whom it was the only neurofibromatous tumour present—in contrast with the above bilateral case in which the tumours are part of the multiple neurofibromatosis syndrome. (W.E.H. case.)

years prior to its classical description in 1882 by von Recklinghausen,[1] is now often known by his name.

The nature of neurofibromatous tumours and of multiple-tumour syndromes in general (pp. 291–3 and 1130) and the origin of the former from the fibrous-tissue elements of the nerve-sheath, are discussed in the general chapter on tumours, under "Fibroma" (p. 301) and "Neurocytoma" ("Neuroma") (p. 315). In a typical case, large numbers of these tumours develop on the subcutaneous peripheral nerves. They commence as small firm fibrous nodules beneath the

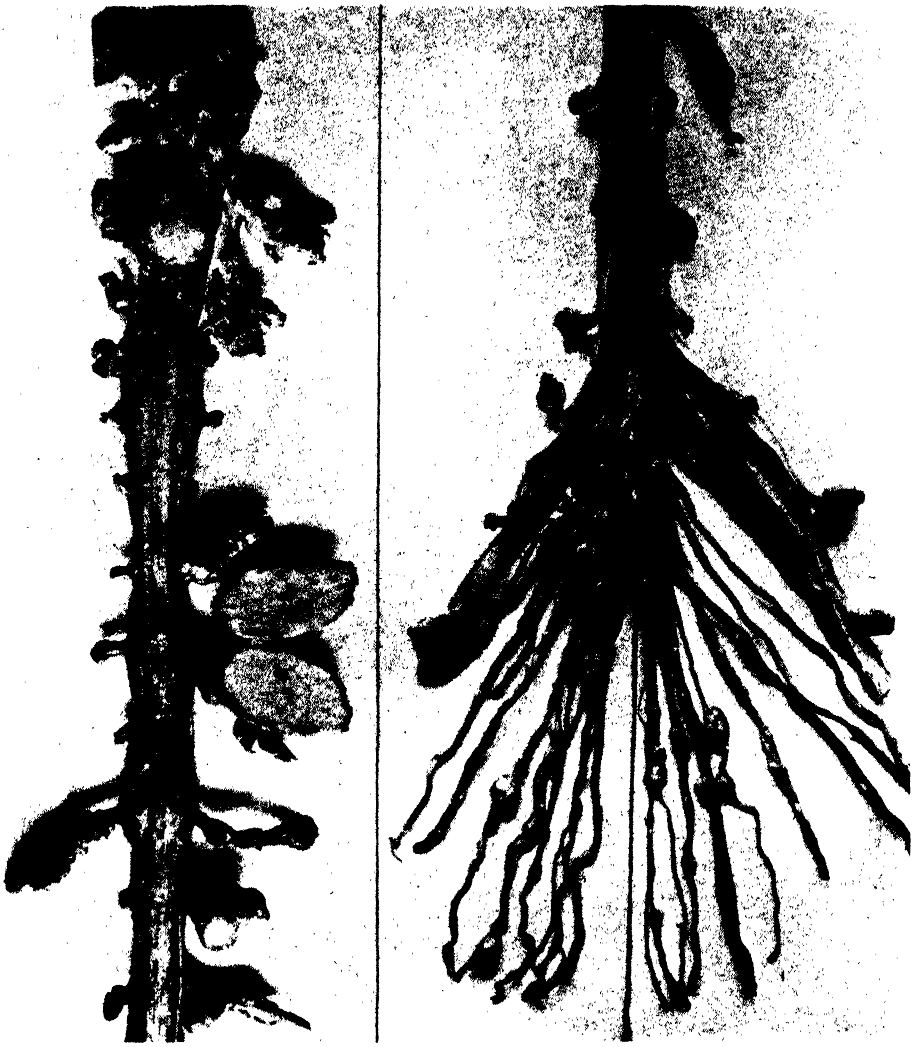
(A) (B)

FIG. 723. *Central neurofibromatosis :* (A) Ventral aspect of the cervical and thoracic regions of the spinal cord, and (B) of the lumbar region and cauda equina of a male aged seventeen years, showing numerous tumours on the nerve-roots and spinal nerves. One of the larger tumours, at the upper part of the cervical enlargement, is seen compressing the cord (*cf.* Fig. 724, p. 1137).

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[1] "Von Recklinghausen's disease" or peripheral neurofibromatosis is not to be confused with the disease of bone, osteitis fibrosa (p. 1211), with which his name has also been associated.

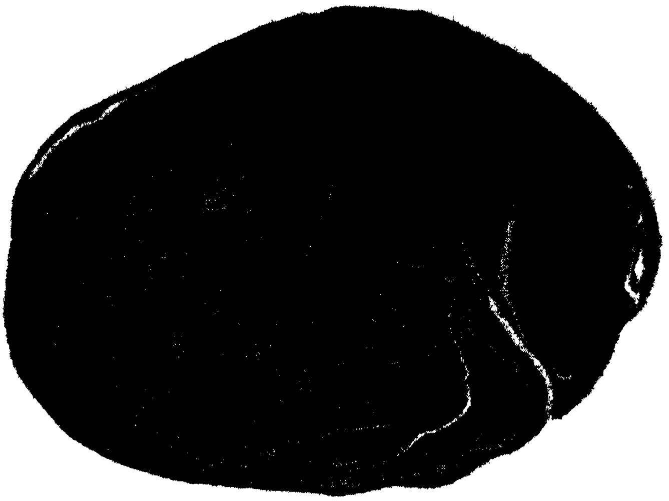

FIG. 724. *Central neurofibromatosis* transverse section through one of the tumours in same case, causing compression and distortion of cord in cervical region—*see* Fig 723 (A), opposite. (Celloidin Section, Weigert Pal's method) × 6

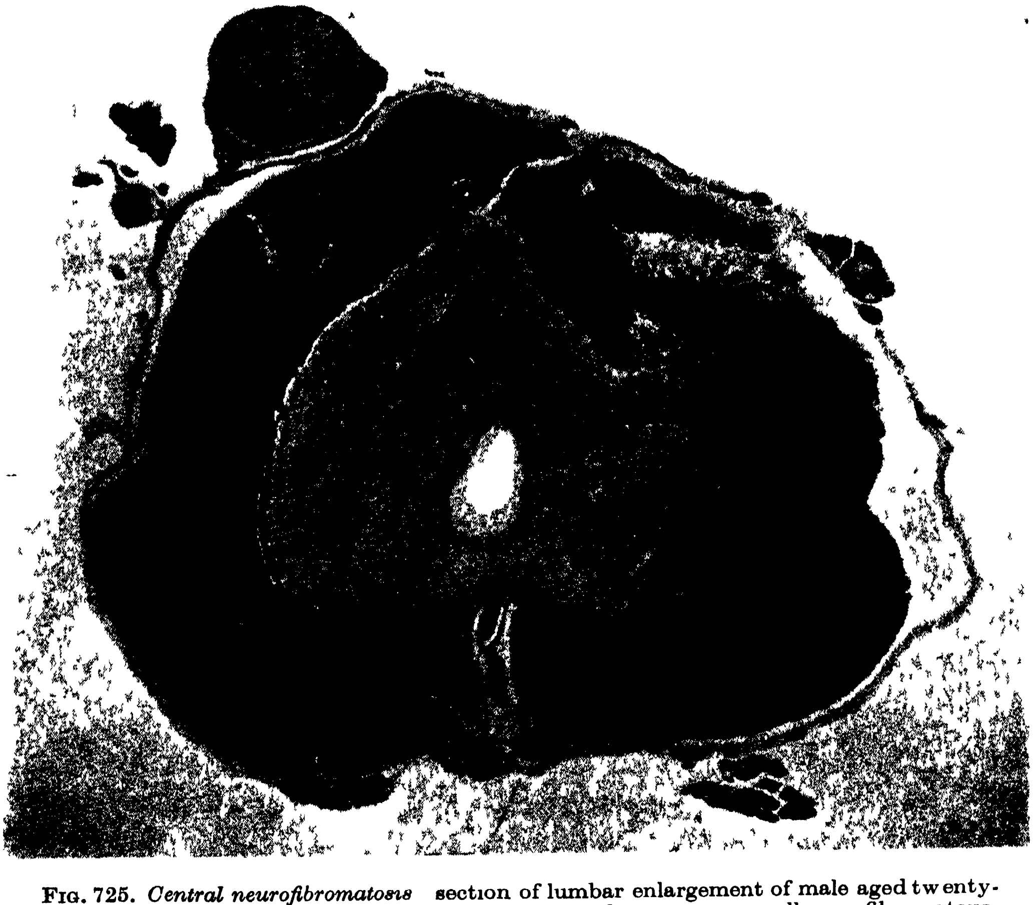

FIG. 725. *Central neurofibromatosis* section of lumbar enlargement of male aged twenty-five years, showing *peri-central gliosis* and *central cavitation* small neurofibromatous tumour on the dorsal nerve-root. Weigert-Pal method for myelin. × 10.

skin, but, as they enlarge, they come to project on and from the skin-surface as rounded or polypoid masses of all sizes, a condition which is sometimes called "**molluscum fibrosum.**" These masses vary, not only in size, but in consistence, and the fibrous tissue of which they are composed may be dense or loose, firm or soft. Though occasionally single, they may vary in number from perhaps a dozen or more up to many hundreds (Fig. 722, p. 1135).

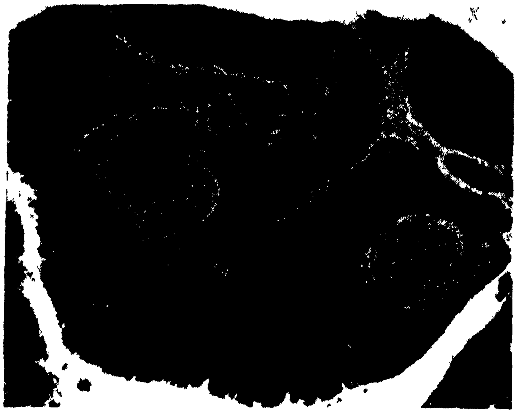

FIG. 726. *Multiple neurofibromatosis:* transverse section of lumbar dorsal root, showing early stage in formation of the tumours as small concentric whorls, reminiscent of those seen in a meningioma (*i.e.*, another form of "nerve-sheath" tumour) and of Pacinian and other varieties of touch-corpuscles. Weigert's hæmatoxylin and van Gieson's method. × 75.

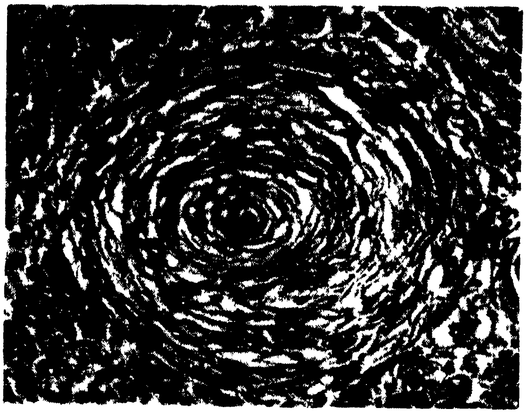

FIG. 727. *Multiple neurofibromatosis* in a man aged twenty-five years. High-power of transverse section of sciatic nerve, showing formation of minute concentrically arranged nodule similar to those found in many of the spinal roots (*cf.* Fig. 726). Hæmatoxylin and eosin. × 400.

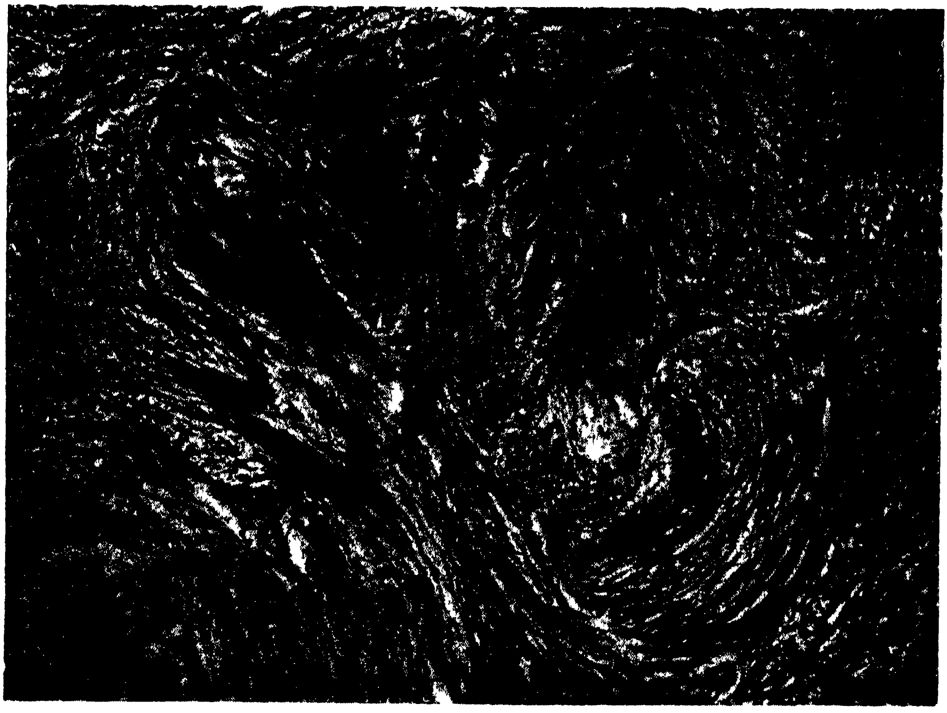

FIG. 728. *Multiple neurofibromatosis:* low-power view of a section of one of the mesenteric tumours present in this case, a male aged seventeen years, showing curving and interlacing bundles and palisading. Van Gieson and hæmatoxylin. × 100.

Multiple neurofibromata occur also on the branches of **visceral nerves,** for example of abdominal organs such as the stomach and intestine (Fig. 728); or on **nerve-trunks** such as the sciatic (Fig. 727), and in sympathetic ganglia (Fig. 769, p. 1198) and suprarenal medulla; whilst in **central neurofibromatosis** they are found especially on *both* acoustic nerves, as bilateral "cerebello-pontine-angle tumours" (Fig. 721, p. 1135). Any of the other cranial nerves, as well as the roots of the spinal nerves may also be the seat of their growth, and in Figs. 723 (A) and (B) are shown characteristic specimens from such cases. In some instances, certain other tumours and congenital abnormalities are associated with general neurofibromatosis either peripheral or central, for example, multiple meningiomata ("Wishart's syndrome") (Fig. 672, p. 1092), syringomyelia-like cavitation and glial, ependymal and vascular proliferative changes [1] (Fig. 725, p. 1137), as well as spina bifida and other abnormalities and deviations of the vertebral column, etc.

Plexiform neurofibroma (*see also* p. 301) is an analogous condition, in which single nerves or groups of nerves are involved, by a more diffuse form of neurofibromatous growth, the regions oftenest affected being the neck, face and scalp.

TUMOURS OF PERIPHERAL NERVES. Some of these have already been considered on pp. 298–301 in the General Chapter on Tumours, and on p. 316, as well as in the above paragraphs on **neurofibromatosis** and **plexiform neurofibroma**; but certain other considerations in connection with their occurrence on **cranial** and **spinal peripheral nerves** require mention.

Theoretically, such tumours may be designated as "**neural**": "**glial**": and "**fibrous**" respectively, according as they are thought to arise from (1) **ectodermic** nerve-elements, *i.e.*, the axons themselves, or from the sheath of Schwann (if it be granted that this is derived from elements of the ectodermic neural crest, and is not merely part of the mesodermic nerve-sheath in general): (2) from the **mesodermic** fibrous tissues of the nerve-sheath, such tumours being derived from any or all of the elements of the peri-, epi- and endo-neurium: and (3) any **combinations of these.**

(1) "**Neural Neuroma.**" The first variety, if derived from the axons themselves, would constitute a true "neur*in*oma" (*see* footnote on p. 1141), but as axons, apart from their corresponding trophic nerve-cells of which they are merely prolongations or processes, have of themselves no power of growth or proliferation, the occurrence of tumours derived from them in the peripheral nervous system is, as far as we are aware, unknown. A unique instance of neoplasia involving true nerve-fibre elements has, however, been described by Alexander Bruce and James Dawson, of Edinburgh, in 1913, in which there was the formation within the white and grey matter of the cord, and also in its membranes, of innumerable small nodules composed of axons, many of them

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[1] These are described in a paper on "Multiple Meningeal and Perineural Tumours with Analogous Changes in the Glia and Ependyma (Neurofibroblastomatosis)," by Worster-Drought, Carnegie Dickson and McMenemey, in *Brain*, 1937, **60**, 85–117. In this paper the relationship of the disease to tuberous sclerosis and other syndrome-diseases, and the light thrown upon the ætiology of these by the recent work on Experimental Embryology and Embryonic Induction of Needham, Waddington and their colleagues in Cambridge are discussed. (In this connection, *see also* p. 291.)

medullated, i.e., neurinomata, for which—as they were dependent for their existence and growth upon their related (trophic) neurone-bodies or nerve-cells, Kinnier Wilson has suggested the term **"neuronoma."** [1]

(2) **"Glial neuroma"** or **"peripheral glioma."** This is a rare congenital tumour, which takes the form of a medullo-epithelioma or neuro-epithelioma (p. 1099, section (1)), of which examples on the median and ulnar nerves have been described by Wilder Penfield.[2] It is less uncommon in the retina (Fig. 680, p. 1099), and occurs occasionally in connection with the spinal cord.

(3) **"Fibrous neuroma"** or **neurofibroma** and **neurofibroblastoma.** This is by far the commonest group of peripheral-nerve tumours and a description of it is included in the section on pp. 298–301 of the Chapter on Tumours dealing with fibromas in general. Neurofibromas may be **single** or **multiple,** and both forms are found upon either cranial or spinal nerves. One of the most characteristic sites for their growth is upon the **acoustic nerve,** as the so-called **"cerebello-pontine-angle tumour."**[3] This may be solitary or unilateral (Fig. 721A); but when bilateral (Fig. 721, p. 1135) is almost always part of the syndrome of central multiple neurofibromatosis (*see* p. 1139). Another characteristic site of the neurofibroma is upon a spinal nerve-root, and if, in this position and as it develops, it grows out through the intervertebral foramen and continues to enlarge both within and outside the vertebral canal, the resulting growth is dumb-bell-shaped—the so-called **"spinal dumb-bell-tumour"** (Fig. 729). This spinal-root form of neurofibroma also may be solitary, or it may be part of a multiple neurofibromatosis; and the instance illustrated in Fig. 729 might be regarded as an example of the minimum possible in a "multiple" case—only two tumours being present.

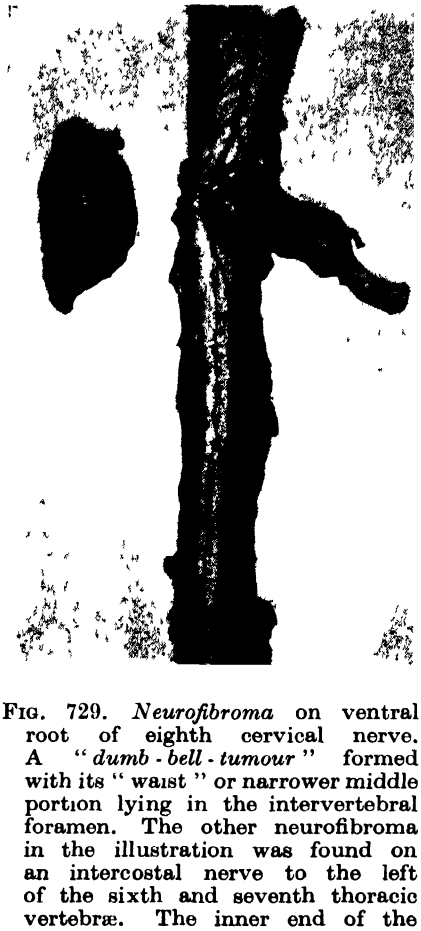

FIG. 729. *Neurofibroma* on ventral root of eighth cervical nerve. A *"dumb-bell-tumour"* formed with its "waist" or narrower middle portion lying in the intervertebral foramen. The other neurofibroma in the illustration was found on an intercostal nerve to the left of the sixth and seventh thoracic vertebræ. The inner end of the tumour on the spinal root caused compression of the cord, and the thecal cerebrospinal fluid below the lesion showed Froin's syndrome (p. 963), total protein being 100 mgr. per 100 c.mm. and cells only one small lymphocyte per c.mm. The patient, a female, aged twenty years, died from acute hæmorrhagic cystitis and *Bact. coli* septicæmia. (W.E.H. case.)

Similarly, fibromatous tumours, solitary or multiple, may occur upon any of the **peripheral nerve-trunks** or their **branches**, whether these be subcutaneous, visceral, muscular or periosteal.

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[1] *Loc cit.*, p. 1323.

[2] "Cytology and Cellular Pathology of the Nervous System," Section XIX, by Wilder Penfield, 1932, pp. 980–4.

[3] Into the controversy as to whether these acoustic-nerve tumours arise from ectodermic glial, or from mesodermic fibrous, tissue, we need not here enter.

After section of nerves, *e.g.*, in amputations or in wounds, the distal end of the central portion of the divided nerve may become swollen and simulate a tumour. On microscopical examination, it is seen that the new formation is composed of **granulation-tissue,** in which there is a limited amount of proliferation of true nervous tissue. These so-called " amputation neuromas " are thus, in the great majority of cases, really the result of an attempt at repair, and are *not* true tumours ; although, in very rare instances, neoplastic growth has been described as supervening upon the reparative processes. In the great majority of instances, the nodular or bulbous thickening developing on the cut end of the nerve consists merely of bundles of nerve-fibrils embedded in an overgrowth of developing fibrous tissue derived from the endoneurium and perineurium. (*See also* pp. 316 and 1178–9.)

Other Tumours of Peripheral Nerves. In addition to the foregoing, a **specific nerve-sheath tumour** was first described by Verocay in 1908 as a " neurinoma," but this has since been re-named more appropriately a **neurolemmoma**[1] by Purdy Stout, of New York, from whose papers on the subject most of the following details are taken. Dr. Purdy Stout points out that this tumour has not yet been sufficiently recognised as a pathological entity, as it is *not* so rare as might be inferred from there having been only about 200 cases of it recorded in the literature. He himself, from his personal experience, describes in his paper no fewer than fifty new cases. Several other names have been given to this tumour, but most of these are best avoided, as they imply belief in some definite histological origin for it—in most instances probably incorrect.[2] The neurolemmoma is usually single and encapsulated, and is composed of well-differentiated tissues characteristic of the nerve-sheath within which it develops. It may, therefore, originate **from endo-**, **epi-**, or **peri-neurium,** and presumably also **from the sheath of Schwann** (though here again the term " Schwannoma " is inappropriate, as the tumour can arise from any or all of these connective-tissue elements of the nerve-sheath). The neurolemmoma is typically a slow-growing and benign tumour, its commonest situations being the **front** of the **upper**, and the **back** of the **lower, limbs,** *i.e.*, on their **flexor** aspects, especially in the neighbourhood of the principal flexion-creases—elbow, wrist or knee. It occurs also on the neck, face and scalp ; much less frequently on the trunk, although the last-mentioned is a common site for the subcutaneous nodules of multiple neurofibromatosis. Neurolemmomas are found occasionally on the nerves of the tongue, stomach and other internal organs and tissues, and also as one variety of the characteristic extra-dural "dumb-bell" or "hour-glass" tumour growing on a spinal nerve-root (Fig. 729), partly within and partly outside the vertebral canal, the constricted part of the tumour occupying the corresponding intervertebral foramen through which it has originally pushed its way and, by its continued growth, given rise to the external portion. A neurolemmoma on one of the larger nerve-trunks may bulge from the side of the nerve, or may expand the tissues of the nerve from within, so that they form an external covering or capsule for the tumour. The nerve-bundles as such are *not* found internal to the tumour-capsule, but a few irregular slender tangled nerve-fibrils may pass into the superficial part of the tumour. They are not found all through the growth, so that surgical resection without much injury to the nerve itself is usually possible. When on a small nerve, the latter may form an inconspicuous thread on or within the substance of the growth, and perhaps be difficult to find. Neurolemmomas are rarely firm and fibrous, and are more often soft in consistence and thus liable to be mistaken for lipomas or for cystic tumours. Two component types of tumour-tissue are described in them : **(type-A)** with narrow wire-like reticulin-fibres in parallel formation and

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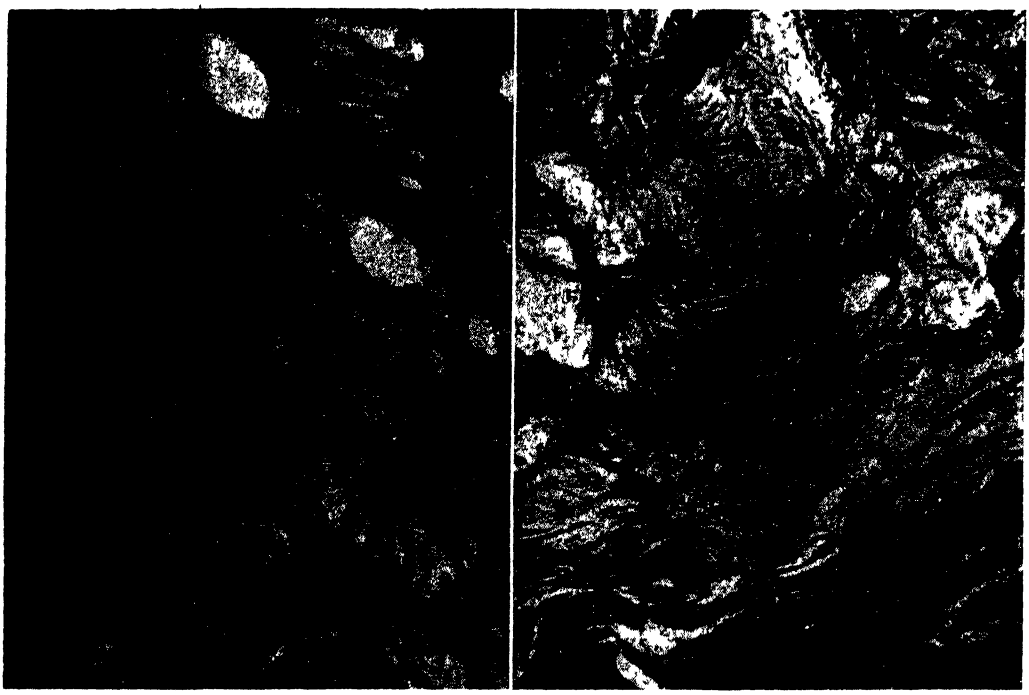
[1] Greek λέμμα, *lĕmma*, a skin or sheath which can be peeled off (from λέπω, *lĕpō*, I strip or peel). Dr. Stout informs us that he believes it to be correct to spell this word with a single " *m* " —" neurilemoma." Readers interested in tumours of peripheral nerves are referred to his authoritative papers on the subject : " The Peripheral Manifestations of the Specific Nerve Sheath Tumor (Neurilemoma)," *American Journal of Cancer*, 1935, **24,** 751 ; and " The Malignant Tumors of the Peripheral Nerves," *ibid.*, 1935, **25,** 1. " Schwann Cell versus Fibroblast as the Origin of the Specific Sheath Tumor : Observations Upon Normal Nerve Sheaths and Neurilemomas In Vitro," by Margaret R. Murray, A. P. Stout and Cloyce F. Bradley, *American Journal of Pathology,* 1940, **16,** 41. We ourselves adopt the spellings " neurolemma " and " neurolemmoma."

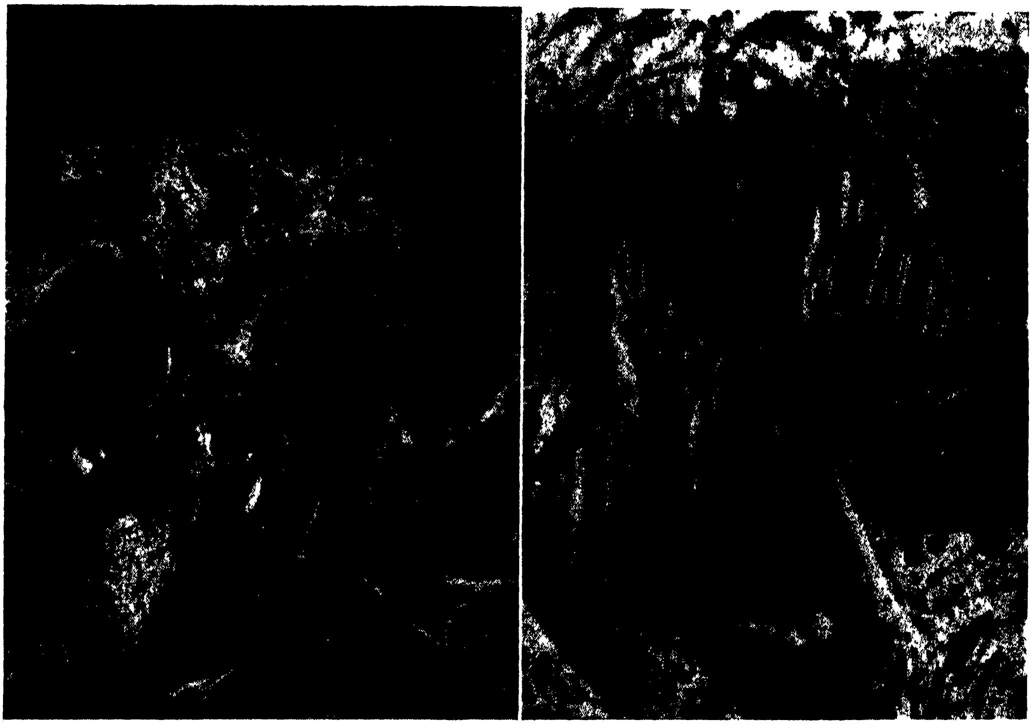
[2] For example the term " neurinoma," unless its actual connotation in this connection is specifically intended, should be avoided, as it implies an origin from the nerve-*fibres* or *axons* themselves. Neur*in*oma = neur-*in*-oma. The Greek word νεῦρον, *neurŏn,* meant originally a sinew or tendon ; in the plural it came metaphorically to mean strength, Latin *vires,* " nerves " ; later it was applied to the fibres of plants ; but not until Galen's time was it used to denote the physical nerves themselves (Liddell and Scott). The word ἴς, ἰνός, *is, inos,* originally meant a muscle (at the back of the neck, *cf.* " inion "), and later came to mean a " fibre." The term " inoma " was introduced by Paget as an alternative term for " fibroma." " Neur*in*oma " therefore means a nerve-*fibre*-tumour (*see also* p. 1139). With regard to the derivation of the suffix -oma, *see* footnote on p. 297.



(1) (2)

FIG. 730. *Neurolemmoma* of small anterior branch of external cutaneous nerve of left thigh in a female aged forty-nine years. Two low-power views showing an admixture of *Type-A* tissue (see text) with characteristic relatively orderly arrangement of long, straight or serpentine, slender wire-like reticulin-fibres in parallel array, blackened by silver-impregnation, and thin-walled vascular spaces : and *Type-B* tissue in which the texture becomes looser, with loss of orientation of the fibres and the formation of microscopic pseudocystic patches of degeneration. (Dr. Colin Edwards' case, W.E.H.) Bielchowsky's silver-impregnation method. × 85.

with a tendency to palisading of the cell-nuclei ; and (**type-B**) with no definite orientation of their fibres or cells, these being loosely and irregularly arranged, often with intercellular collections of degeneration-products giving rise to the formation of minute pseudocystic spaces. Collagen-bands, except immediately around some of the blood-vessels, are scanty or absent. Varying admixtures of type-A and type-B tissues go to build up the individual tumours. Blood-vessels are irregularly distributed, scanty in some areas, abundant in others. They may have characteristic thickened and hyaline walls, as shown in our illustration (Fig. 731 (3)) ; or be dilated and thin-walled, and from the latter hæmorrhages are common.



(3) (4)

FIG. 731. *Neurolemmoma :* low and high-power views of sections from same specimen as shown in Fig. 730. In (3) a patch of *Type-B* tissue is seen, containing a small artery with a thickened hyaline collagenous sheath. The transition from the surrounding *Type-A*. tissue to this more loosely-textured *Type-B* patch is abrupt. In (4) the " palisading " of the long tapering cells of *Type-A* (their intervening reticulin-fibres are shown in Fig. 730) and the grouping of the nuclei towards their blunt ends, is well seen, and also the tendency of the elongated and branching cell-bodies to coalesce and form a syncytium. All four of these illustrations conform closely to the descriptions of this tumour in Dr. Purdy Stout's paper. (3) Masson's trichrome stain. × 85. (4) Mallory's connective-tissue stain. × 350.

Malignant tumours of peripheral nerves (including the extradural portions of the cranial nerves, except the optic nerves which are part of the central nervous system), are by Purdy Stout divided into the commoner **fibroblastic** tumours and the rarer **neuro-ectodermal** group. The former include the **fibrosarcomas,** most examples of which are found in individuals already suffering from neurofibromatosis, of whom some 10 per cent. are liable to develop them. These fibrosarcomas are radio-resistant and tend to reappear after attempted removal, no case of surgical cure having yet been reported, probably because of the presence of much more extensive spread along the affected nerve than had been suspected clinically or than the naked-eye examination of the tumour would seem to indicate. The " reappearance " after what had been thought to have been sufficiently wide excision or amputation takes the form of nodules in the severed nerves, *e.g.*, in the amputation-stump. Fibrosarcomas of nerve develop into rounded or spindle-shaped masses, sometimes attaining the size of an adult head or larger, although interruption of the nerve-fibres themselves is uncommon. Except for the characteristic spread along the nerve itself, the tumour does not tend to infiltrate neighbouring tissues, *e.g.* laterally. The cut surface is pale grey and homogeneous, or may show a " watered-silk " interlacing fibrous appearance like that seen in a uterine fibromyoma. Most of these fibrosarcomatous tumours consist of long closely-packed spindle-shaped cells in interweaving bands or cords running in various directions, with abundant reticulin- or collagen-fibres, or both of these, separating each cell from its neighbours—the picture characteristic of a fibrosarcoma (pp. 275–7 : and p. 316 *et seq.*). When loose-textured and œdematous, the structure comes to resemble that of a " myxoma," but Purdy Stout has not detected mucin in them and is doubtful as to the accuracy of their being so designated.

The uncommon **malignant neurofibroma** preserves and reproduces the pattern of the simple neurofibroma but with continued and unlimited growth.

Malignant neuro-ectodermal tumours (neuro-epitheliomas) of peripheral nerves are, as noted in section (1) on p. 1099, uncommon, and Purdy Stout suggests that they arise either from the Schwannian syncytium or from congenitally misplaced neuro-epithelium of the neural crest, with the development in them of epithelial-lined cysts (p. 1099).

Gangliomas arise from the ganglia on the course of cranial and other nerves, *e.g.*, the vagus (pp. 845–7 and 1114–18) : and **paragangliomas** from the paraganglia associated with the sympathetic trunks and plexuses and elsewhere. (*Cf. also* under " Carotid-Body Tumour," p. 849.)

SECONDARY GROWTHS IN THE CENTRAL NERVOUS SYSTEM

Metastases affecting the central nervous system are by no means rare. **Local invasion** by malignant tumours of the skull and vertebral column—these tumours themselves being often secondary to primary growths elsewhere—are described under diseases of bone (p. 1232). Apart from involvement of the meninges and ventricular system by " seeding " in the instance of medulloblastomas (pp. 1099–1102): and of the brain or the opposite eye by growths secondary to certain tumours of the retina, metastases, from even actively infiltrating, *i.e.*, locally malignant, members of the glioblastoma-neuroblastoma series (apart from those of the suprarenal medulla and peripheral ganglia—p. 846), are of exceptional rarity.

Carcinoma of the prostate and **breast** are of importance in connection especially with the production of secondary tumours in the spine, and these not infrequently produce pressure upon, or invasion of, the cord, either by direct spread or by metastasis (Figs. 542, p. 914, and 732, opposite). Spread from pelvic and abdominal malignant tumours by way of the intercommunicating **venous** plexuses—as well as by **lymphatic channels**—is also, we believe, a common method of dissemination. For example, in the instance of carcinoma of the prostate (Fig. 539, p. 913), secondary growths may be formed, not only in lymphatics and lymph-nodes (Fig. 540, p. 913), but in and in relation to the prostatic venous plexus and rich intercommunicating network of veins connected with the vertebral column.[1] In this network are included the veins from and in the vertebral bodies themselves, as well as the spinal and intercostal veins (within which, it has been suggested that, on any sudden increase of intra-abdominal or intra-thoracic pressure, a temporary retrograde flow of the contained blood may be produced, carrying with it in such cases any malignant cells present in it). Thus, in cancer of the breast, metastases may be carried, not only by lymphatics (pp. 947–8), but by the intercostal and vertebral veins to the bodies of the vertebræ. In both prostatic and mammary cancer, we have often observed what we believe to be this mechanism of spread ; and in both, whether the carriage has been by lymphatics or veins, we have not infrequently found metastases in the upper and posterior part of the dome of the chest-wall —usually in the substance of the ribs—as well as in the vertebral and cranial bones ; and, from the latter, the meninges and the neuraxis itself may then come to be involved.

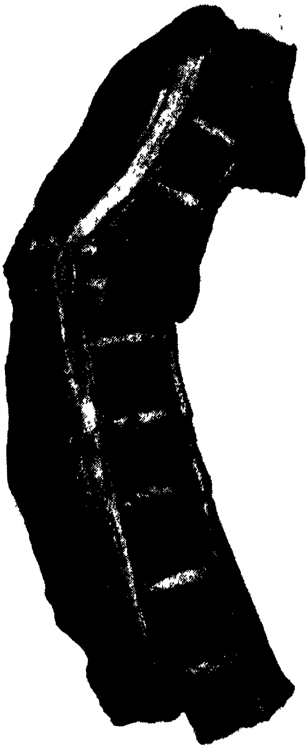


FIG. 732. *Metastases in bones of vertebral column secondary to mammary carcinoma,* causing collapse and " angular curvature " resembling that of Pott's disease (*cf.* Fig. 600, p. 999), with compression of the spinal cord. (W.E.H. case.)

Malignant tumours of the pineal and pituitary bodies occasionally give rise to metastases elsewhere within the skull. The occurrence of " malignant papilloma of the choroid plexus " has been described by some writers, but many (if not the great majority) of the instances so recorded have in all probability been

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[1] " The Spinal Veins and Metastases," *Brit. Med. Jour.*, " Annotation," 1941, i, 284, referring to Professor Oscar V. Batson's work (*see* p. 171 and footnote to it).

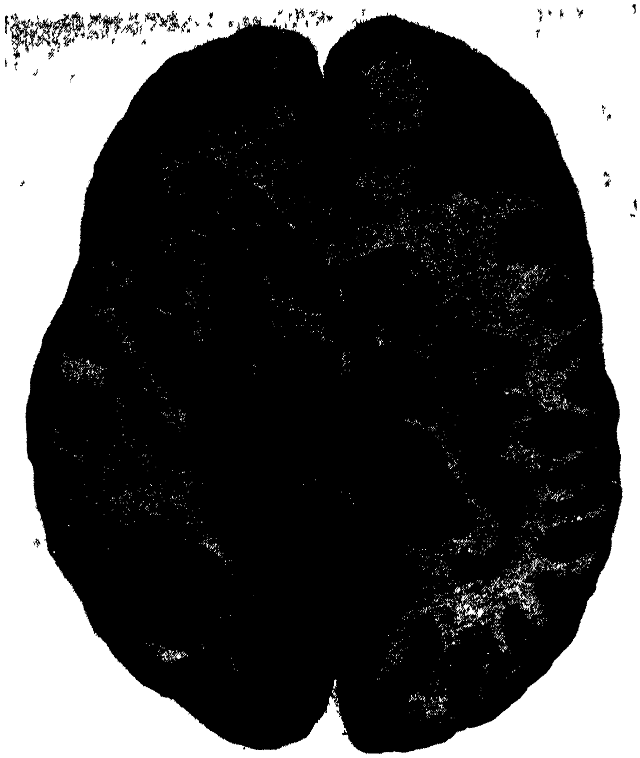


FIG 733 *Bronchial carcinoma* · *metastases* simulating papilloma of choroid plexus: several secondary tumours in the brain of a man (case (B) in Figs. 349 and 351, pp. 570 and 573) aged 55—one, in continuity with right lateral choroid plexus, invading ventricular wall and corpus callosum. The nodule in the left occipital lobe shows development of a cystic cavity *not* part of the ventricle.

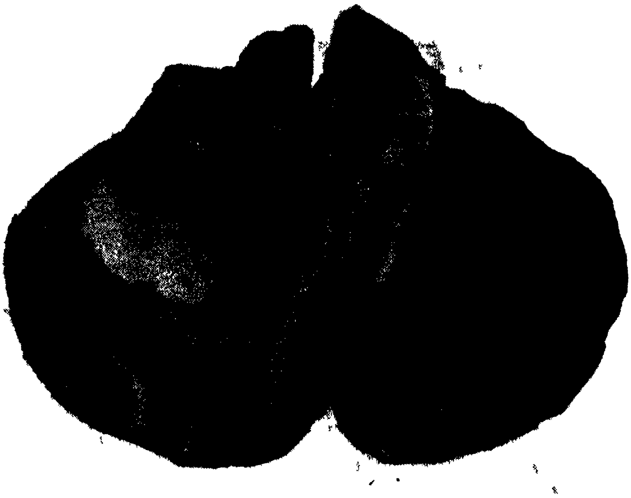
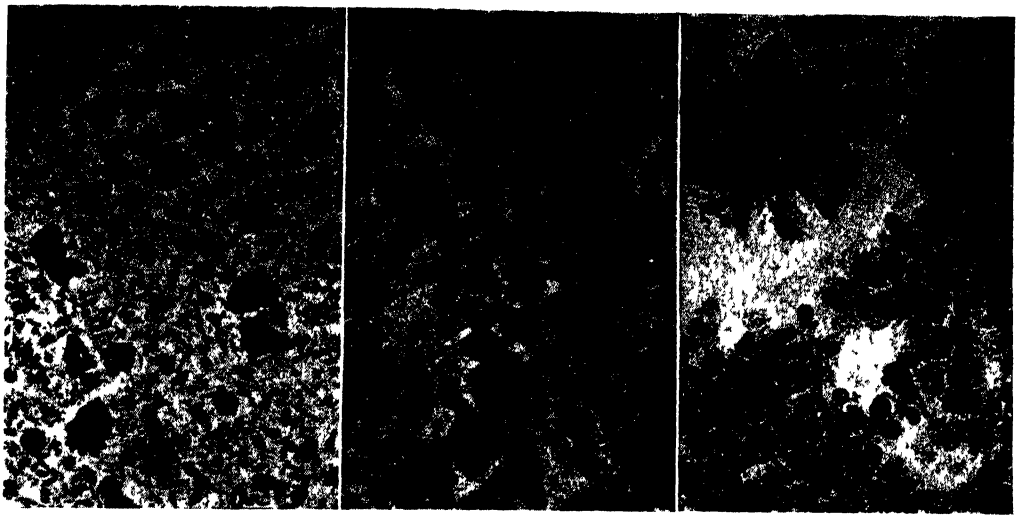


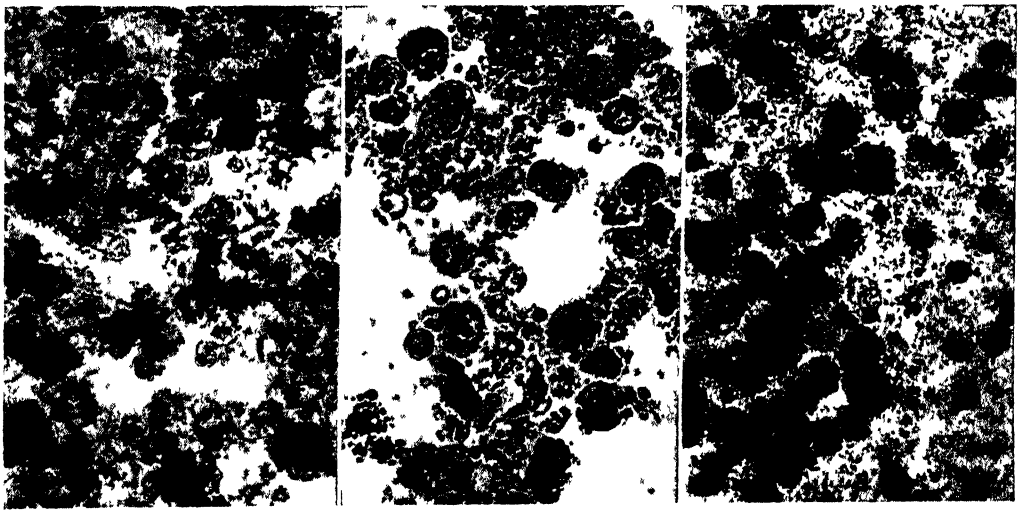
FIG. 734. *Bronchial carcinoma with metastases in brain:* horizontal section through cerebellum of same case, showing numerous secondary nodules of the spongy papillomatous tumour. In connection with the largest of these growths several cysts, of considerable size, have developed, the contents of which very much resemble mucoid sputum.



(A) × 75 (B) × 300 (C) × 30

FIG. 735 *Bronchial carcinoma metastases in brain*

Fresh-wet toluidin-blue preparations of diagnostic puncture fluids from three cases in which craniotomy was performed for the relief of pressure The lung condition was so inconspicuous as to be completely overshadowed by the cerebral symptoms Examination of these films enabled the pathologist to make an immediate provisional diagnosis of " malignant tumour probably metastases from a primary bronchial carcinoma ", and to indicate to the surgeon that any attempt at removal appeared inadvisable Papillomatous fragments and epithelial cells suggestive of " bronchial catarrhal cells" were found in a fluid containing mucin (*cf* Fig. 351 (*d*), p 573 and *contrast* with Fig 736, below, from a secondary growth of mammary carcinoma in the brain (W E H cases.)



(D) (Toluidin blue) (E) (Methylene blue) (F) (Sudan III)

FIG. 736. ***Fresh-wet preparations of a diagnostic puncture-fluid from a cystic metastasis in the temporal lobe from a mammary cancer*** **in a woman of forty-seven, whose breast had been removed two years previously for scirrhous carcinoma. The semi-solid contents of the cyst consisted largely of** ***fatty globules and debris,*** **both free and within degenerating tumour-cells. The reaction for mucin was negative, and the large amount of fat present suggests the possibility of its aberrant, if also degenerative, production by tumour cells derived from an originally milk-secreting epithelium. × 300.**

secondary to some undetected primary bronchial or other variety of carcinoma (p. 569 *et seq.* : and Figs. 351 and 733, pp. 573 and 1146).

Bronchial carcinoma is the commonest and perhaps the most important source of secondary growths in the brain, its dissemination, like that of infective material from an abscess or bronchiectatic cavity in the lung, being by way of the pulmonary veins and left side of the heart, and then by the arterial circulation to the brain. Some of its characters are described on pp. 572 to 576, and, from our present point of view, the " latency " of the symptoms of the pulmonary lesion in a considerable proportion of cases, especially in male patients, may again be emphasised here as one of its most outstanding features, these cases often first coming under observation with a diagnosis of " tumour of the brain " (p. 574), the symptoms of the lung-condition having been overlooked or regarded, perhaps, as due merely to a " chronic bronchitis " or "an attack of asthma." Another point of importance is that these secondary growths in the brain are almost always (though, as pointed out on p. 574, not invariably) **multiple**—an essential consideration if any operative interference, other than a mere decompression for the relief of pressure-symptoms, is in contemplation. Allusion has also been made to the tendency of the

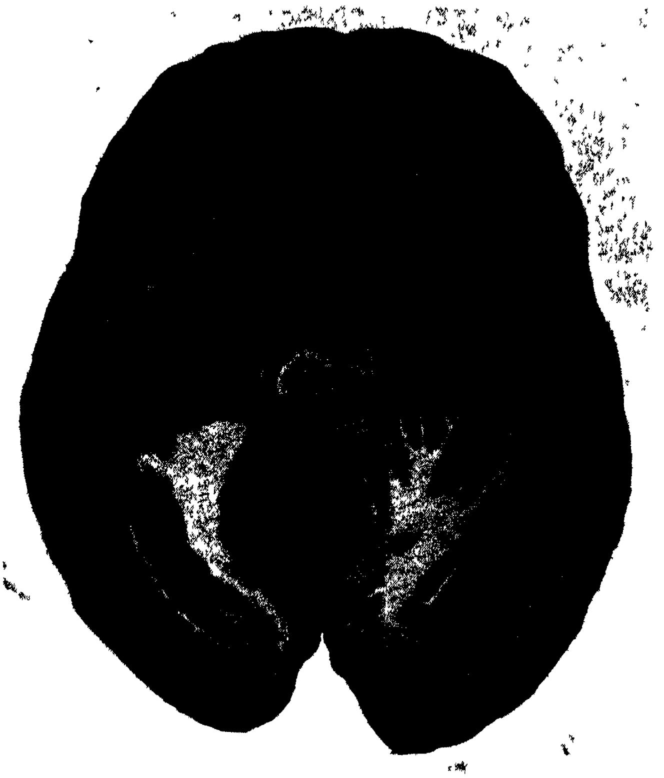


FIG. 737. *Metastasis of bronchial carcinoma in cerebellum* of a man aged fifty-one years. This specimen, like that illustrated in Fig. 738, is *exceptional* in being the only metastasis present in the brain. The primary tumour was of large size, occupying most of the upper lobe of the left lung, and this cerebellar metastasis shows the characteristic spongy appearance of such growths, containing numerous small cysts, often mostly microscopic. (Dr. Yealland's case, W.E.H.)

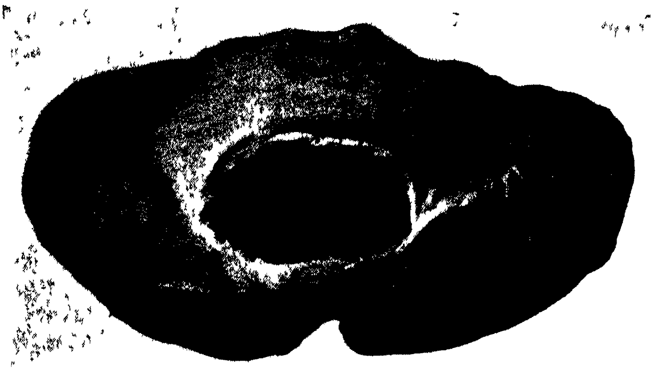


FIG. 738. *Metastasis of bronchial carcinoma in cerebellum* of a man aged sixty-eight years : showing a single large central cystic cavity formed by the breaking-down of the main mass of the tumour, leaving only a thin wall of surviving malignant tissue. The tumour was situated immediately above the fourth ventricle and caused a considerable degree of internal hydrocephalus. This specimen, like that illustrated in the preceding Fig. 737, was *exceptional* in that the involvement of the brain was *not* multiple, this cyst being the only intracranial growth found. (Dr. Yealland's case, W.E.H.)

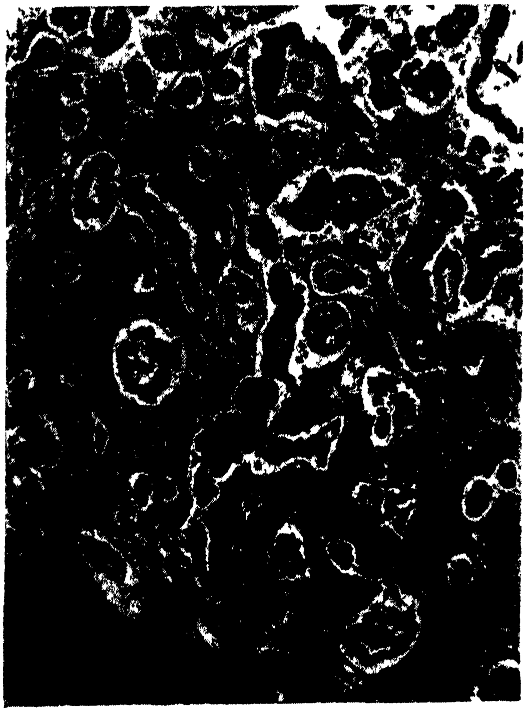


FIG. 739. *Metastasis of bronchial carcinoma in the brain* of a man aged forty-five years : low-power view of the *spreading margin* of a secondary papillomatous tumour, to illustrate the diffuse nature of the infiltration of the surrounding brain-tissue by the tumour-cells. In the literature,[1] there are records of such tumours having occasionally been thought, when their malignant nature had not been recognised, and because of their soft spongy character, to be " easily enucleable " ; but the nature of the spreading margin here illustrated indicates the practically hopeless prognosis in such cases. (W.E.H. case.) Hæmatoxylin and eosin. × 75.

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[1] For references *see* Carnegie Dickson and Worster-Drought, *loc. cit.*, p. 291. *See* footnote on p. 574.

metastases derived from bronchial carcinomas to take on papillomatous characters, and also to show the development of cystic cavities, small or large, as illustrated in Figs. 351 and 354 (A) on pp. 573 and 575, and also in Figs. 733–4 and 738 on pp. 1146 and 1149. The results of **exploratory puncture** as a help to the diagnosis of cerebral metastasis from bronchial carcinoma are illustrated in Fig. 735 on p. 1147; and these are contrasted with findings obtained from biopsy-specimens from metastases from carcinoma of the breast (Fig. 736, pp. 1147).

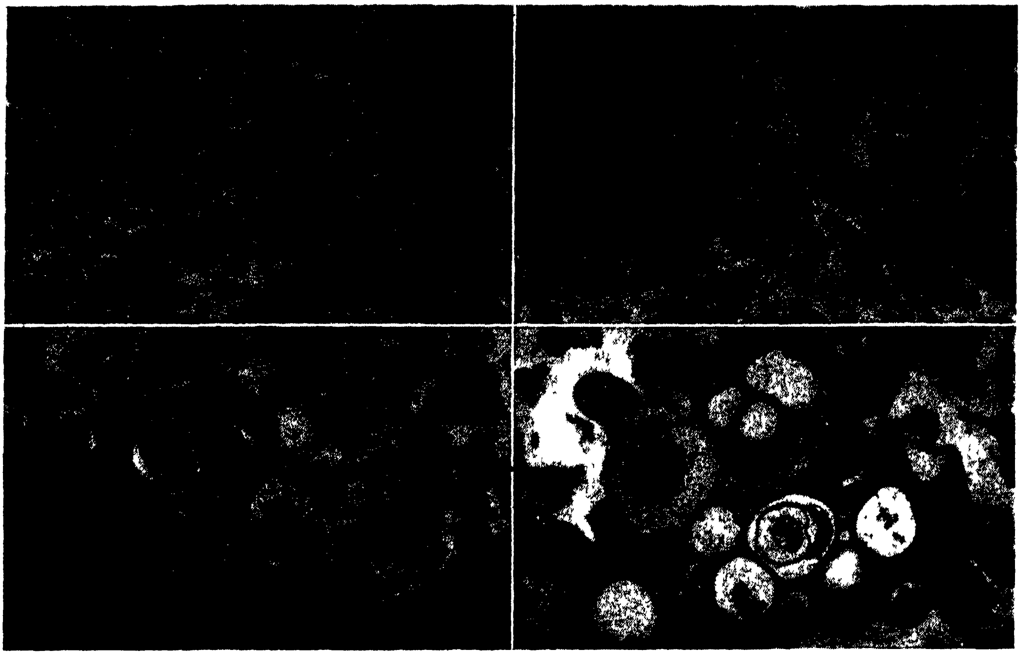

FIG. 740. *Bronchial carcinoma : metastasis in brain :* section from periphery of a large nodule at left occipital pole, showing rather loose and slightly papillomatous structure and a tendency to squamous metaplasia, together with very active phagocytosis of the tumour-cells by each other. Hæmatoxylin and eosin. Low power, × 75. High power, × 300.

The occurrence of cerebral metastases is described as characteristic also of "hypernephromas," but in this connection the reader should refer to p. 895, where it is explained that tumours so called are usually **renal carcinomas. Chorionepitheliomas** (pp. 352–3 : and Figs. 550–2, pp. 925–6) derived from the fœtal part of the placenta, and the analogous teratoid tumours of the testicle (Figs. 533 to 536, pp. 909 and 910), themselves rare neoplasms, have, in a considerable proportion of cases, given rise to rapidly growing secondary growths in the brain, as well as in the lungs and liver.

Malignant melanomas, now usually regarded as carcinomatous rather than "sarcomatous"[1] in nature (pp. 323–4), whether they arise in the eye (itself part of the central nervous system) or in the skin, may lead to the production of innumerable metastases throughout the neuraxis.

Sarcomas of the bones of the skull or vertebral column or of the membranes of the brain or cord, whether primary, or secondary and derived from elsewhere, may invade or give rise to further secondaries in the brain or cord, but amongst these should *not* be included the spread of medulloblastomas by "seeding" (pp. 1100–1), sometimes mis-named "sarcomatosis" of the membranes.

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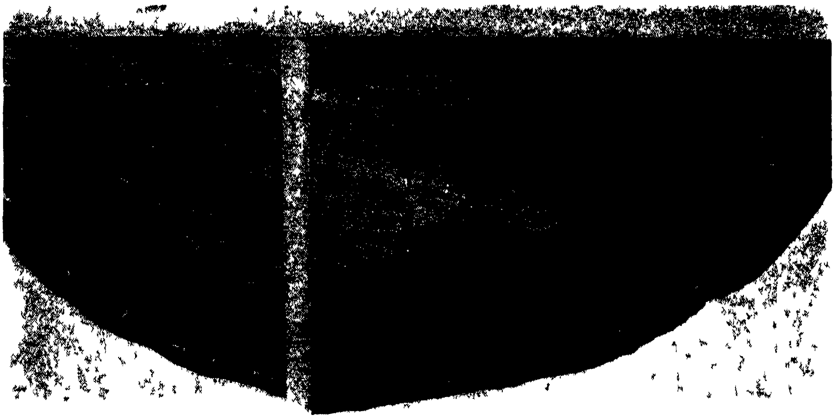
[1] But, in this connection, *see* Fig. 677 (A) and (B), p. 1095, which illustrate a melanoma arising in the outer part of the spinal dura—a pigmented tumour in which classification as a "carcinoma" presents certain difficulties.

Secondary growths of the so-called "oat-celled" varieties of bronchial carcinoma (p. 571) have in various instances been mistaken for "endotheliomas" or "sarcomas." **Sarcomatous metastases** in the central nervous system are, however, much rarer than the carcinomatous; and a series of about 300 post-mortems on cases of intracranial tumour examined at the West End Hospital for Nervous Diseases, London, has not included any of these, with the exception of a couple of cases of chondro-sarcoma of the base of the skull, which indented, but did not invade, the brain.

ANIMAL PARASITES. Of **worm-infestations** of the nervous system, **cysticercosis of the brain and eye,** due to the presence of the larval cysts of *Tænia solium* (p. 394) is, since the work of MacArthur[1] at Millbank (1924 and 1934), now recognised as less uncommon and more important than was formerly supposed. When previously healthy and often comparatively young soldiers, especially any who have been abroad, for example in India, have been invalided out of the service because of "epilepsy," the diagnosis in many cases has, on further investigation, proved to be an infestation with cysticerci. The **epileptiform fits** have usually been accompanied by severe and otherwise unaccountable **headache** and various obscure nervous symptoms. In fatal cases, sometimes as many as 300 or 400 cysts have been found in a single



(A) (B)

FIG. 741. *Cysticercosis of brain* in an ex-soldier aged twenty-eight years, who at the age of eighteen enlisted and was sent to India. In the occipital cortex (A) are seen one semi recent shrivelled, and two old degenerated, cysticerci, whilst in the frontal cortex (B) are shown a couple of more recent cysts and another, cut tangentially, situated in the white matter just beneath the cortex. The patient had previously had an eye removed for cysticercus-infestation, and had suffered from epileptiform fits and increasing mental dullness. (Dr. Worster-Drought's case) Three-quarters natural size.

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[1] "Cysticercosis as seen in the British Army, with special reference to the Production of Epilepsy," by W. P. MacArthur, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1933–34, **27**, 343 *See also* "Epilepsy in Cysticercosis (*Tænia solium*). A Study of Seventy-one Cases," by H. B. F. Dixon and D. W. Smithers (Millbank), *Quart. Jour. Med.*, 1934, **27**, 603; and "Cysticercosis of the Brain with Epilepsy and Papillœdema," by W. E. Carnegie Dickson and J. D. Willis (W.E.H.), *Lancet*, 1941, ii, 415, from which paper Figs. 741 to 744 here, and Figs 213–14 on p. 396, are reproduced by kind permission of the Editor.

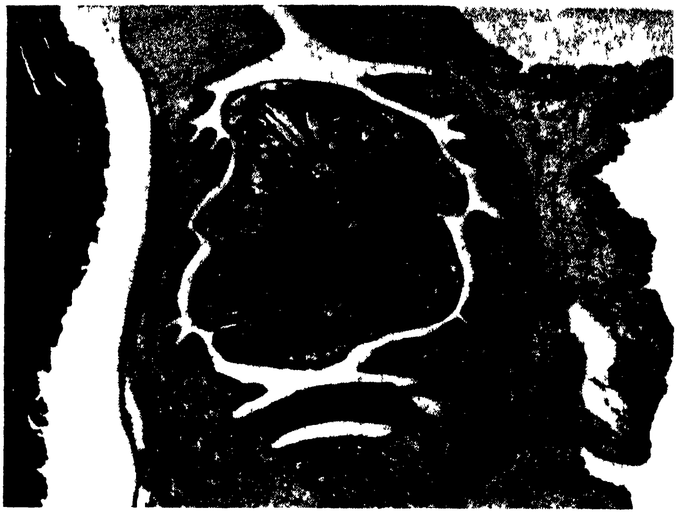

FIG. 742. *Cysticercus-stage of Tænia solium :* biopsy-specimen from lumbar muscles in a case of general cysticercosis in a soldier, aged 32, who developed epilepsy on his return from India (*see also* Figs. 213–4, p. 396). Oblique section of scolex, passing through two of the four suckers, and base of the rostellum with its armature of hooklets and its musculature. Part of the semi-calcified external fibrous-tissue wall is seen at the left-hand margin. Mallory's connective-tissue stain. (Drs. Carnegie Dickson, Neill Hobhouse and J. D. Willis's case. W.E.H.) × 75.

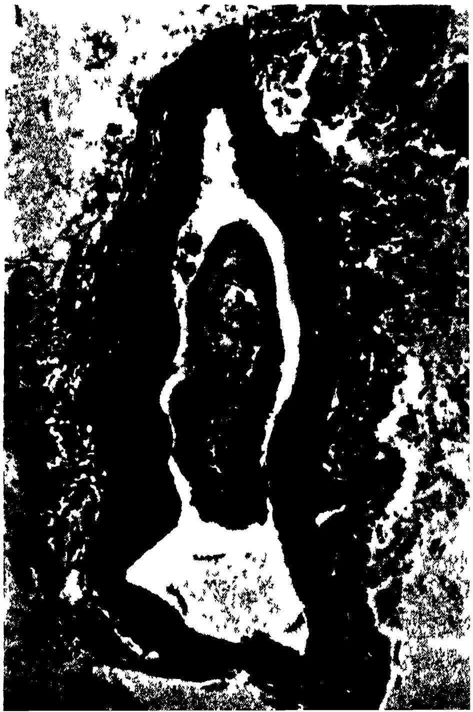

FIG. 743. *Cysticercus from the brain :* biopsy-specimen from the same patient as in Fig. 742. This cyst is degenerated and partially calcified, and contains a dead scolex, the degenerated appearance of which contrasts with that of the living scolex from the same case illustrated above in Fig. 742. The cyst was one of several removed from the hand-area of the right motor cortex, and was probably ruptured and had become partially collapsed during its surgical removal (*cf.* the unruptured degenerated cyst illustrated in Fig. 744, opposite). The patient had suffered from epilepsy for two and a half years, with headache and papillœdema. (W.E.H. case.) Mallory's connective-tissue stain. × 25.

brain ; and there has, as a rule, been no history of any previous intestinal tapeworm-infestation. Almost all the cases recorded in this country have been in soldiers, or in soldiers' families. MacArthur is probably justified in believing that serious cerebral symptoms supervene as a rule only when **death and degeneration of the larvæ have themselves** taken place, as an increase in size of the cysts then tends to be produced by imbibition of fluid. Whilst the parasite is still alive, it becomes surrounded by a zone or capsule of thickened and proliferated glial, and a varying amount of fibrous, tissue, and, unless the cysticercus is in some specially vital position in the brain, a species of symbiotic harmony between parasite and host appears to be established, which may last for several, and perhaps for many, years. As serious pathological results thus in many instances may ensue only on the death of the parasites, attempts at killing them off by drugs must as yet be regarded as ill-advised, as is also the

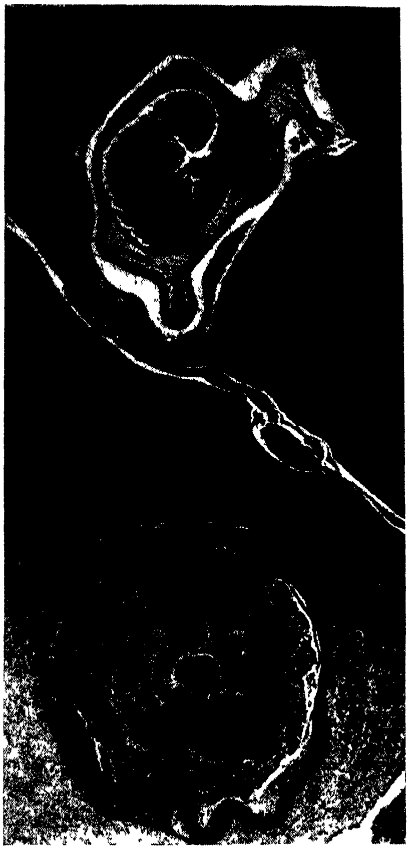

FIG. 744. *Cysticercosis of the brain :* paraffin-section through two adjacent specimens of the bladder-worms of *Tænia solium*, the pork-tapeworm, from the frontal cortex of a soldier home from India, who died at the age of twenty-eight, after suffering from epileptiform fits and cysticercosis of the left eye for six years. (1) The upper specimen is a well-preserved and " healthy " or " symbiotic " scolex (details of the structure of which are illustrated in Figs. 213–14, on p. 396). (2) The lower specimen in the figure is an example of a *dead and disintegrating parasite* showing accumulation of fluid around it, *i.e.*, the stage at which it becomes more irritative and dangerous to its host. (Dr. Worster Drought's case. W.E.H.)
Mallory's connective-tissue stain. × 15.

attempted surgical removal of the cysts in the brain, unless they are causing serious symptoms on account of their position : or if, as in the case illustrated in Fig. 743 on p. 1152, the eyesight is threatened by the occurrence of papillœdema. As the larvæ often survive in this way "symbiotically" for a number of years, the more active destructive and necrotic changes around them leading to the epileptiform seizures may not come on until after a considerable "latent" period. If the death of the patient does not occur, **a zone of glial and fibrous-tissue sclerosis** is formed ; and **calcification,** commencing either in the scolex, or more frequently in the cyst-wall, tends to supervene—perhaps only after three or four

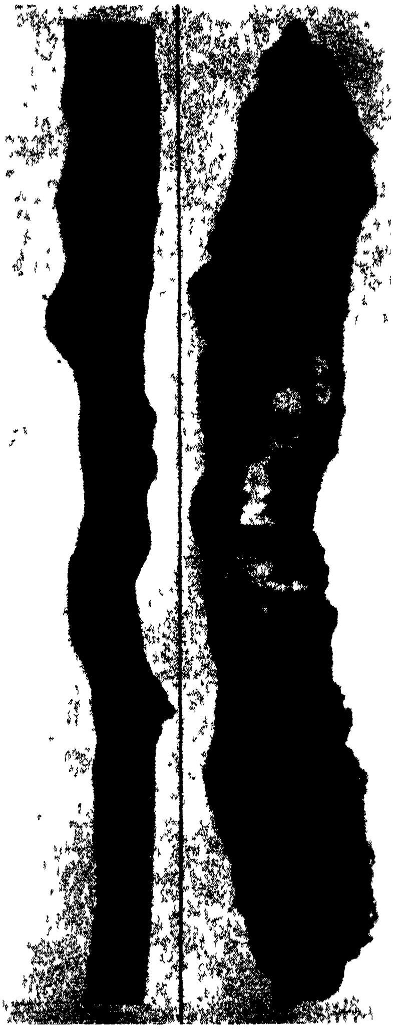

Fig. 745. *Recurrent paraplegia due to hydatids* in a girl who died aged thirteen-and-a-half years. Spinal cord after removal, showing cervical and thoracic regions. There is much inflammatory thickening, especially around the cervical enlargement. The cord itself was so soft that its removal was a matter of great difficulty. On the right is shown the strip of neural arches and inflammatory tissue, excised for the removal of the cord, with a number of semi-collapsed hydatid-cysts on its ventral (deep) surface where they lay between the bone and cord. (Worster-Drought and Carnegie Dickson's case, W.E.H.) Three-quarters natural size.

years—and X-ray diagnosis may only *then* become possible. At this late stage in the development of the disease, the occurrence of eosinophilia in the blood is exceptional, and specific serum-reactions have often become negative.

Hydatid-cysts (p. 400), the larval form of *Echinococcus granulosus* (*Tænia echinococcus*), are also usually multiple, and may invade the brain, and, more rarely, the vertebral canal and spinal cord (Fig. 745).

In **trichiniasis** or **trichinelliasis** (p. 417), the nervous system is not infrequently involved, symptoms appearing in some two to six weeks after the original infestation.

Meningitic symptoms, with varying degrees of pleocytosis and protein-increase in the cerebrospinal fluid, may be found in individual cases of all three of these worm-infestations, more especially in cysticercosis; but, in the majority of patients with **trichiniasis,** the cerebrospinal fluid tends to remain unaltered, although the symptoms may simulate those of a coccal meningitis, *e.g.*, head-retraction and photophobia, Kernig's sign and extensor plantar responses; and the patient may become sluggish and lethargic or perhaps comatose, or sometimes melancholic and subject to delusions. Some cases (17 per cent. in one series[1]) show evidence of the presence of focal damage to the brain, such as monoplegias or cerebellar ataxic symptoms. Hæmorrhage under the finger-nails was noted in as many as 10 per cent. of Sheldon's cases, and this curious sign had previously been noted by J. B. McNaught (1939) in America.

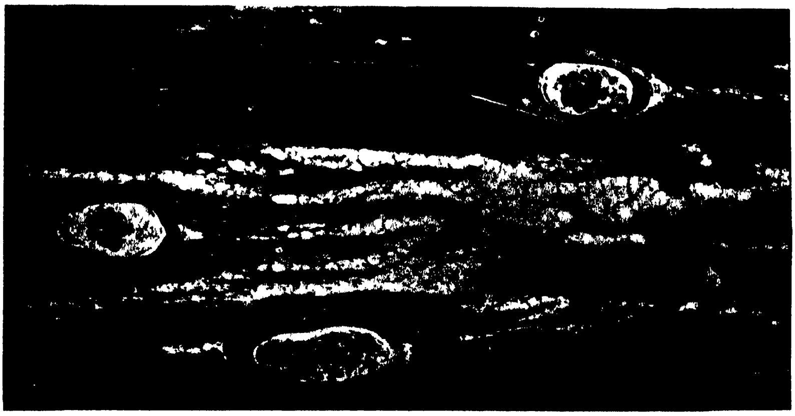

FIG. 746. *Trichinella-embryos* encysted in human muscle. ×40.

PROTOZOAL INFESTATIONS. In "malignant" forms of **malaria,** cerebral types of the disease, both acute and chronic, occur—the former especially in children. The capillaries of the brain become distended and often blocked by large numbers of red corpuscles containing the parasite, *Plasmodium falciparum* or *Laverania malariæ* (p. 380). Considerable quantities of pigment accumulate in the lumen and within the vascular endothelial cells; and the extensive obstruction of these small vessels gives rise to serious and perhaps fatal results. Small areas of necrosis and hæmorrhage around the capillaries may also be found. The cerebrospinal fluid contains an excess of lymphocytes and protein. In **general paresis,** the histological results upon the brain itself of **therapeutic inoculation** with *Plasmodium vivax* require further detailed investigation before any definite pronouncement can be made as to their nature and extent. Recent work seems to show that the efficacy of the treatment depends upon an induced spirochæticidal reaction, and is in no way due to any restitution of the nervous tissues already damaged.

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[1] "An Outbreak of Trichiniasis in Wolverhampton and District," by J. H. Sheldon, *Lancet*, 1941, i, 203.

Secondary entamœbic abscesses, as a complication of **tropical dysentery** (pp. 363, 748 and 778), occur occasionally in the brain, and *Entamœba histolytica* has been demonstrated in their walls.

Trypanosomes are found in the cerebrospinal fluid in many cases of **sleeping sickness** (p. 369), together with a very variable, and, it is said, a more or less parallel, cell-count of from 5 or 6 up to 2,000 cells, chiefly lymphocytes, the parasites being demonstrable, as a rule, only when there is also a definite pleocytosis. The amount of total protein is also variable—up to perhaps 100 mgr. per 100 c.cm.

SECTION XIII

DEMYELINATING DISEASES

These are a heterogeneous series of often more or less unrelated diseases or disorders characterised by the occurrence of patches—localised or widespread—irregular, or sometimes perivascular, in their distribution, of **myelinoclasis** or the destruction of the myelin-sheaths of certain nerve-fibres. These disorders may be classified somewhat arbitrarily into the following four groups, according as they are associated predominantly with [1] :—

(1) **Nutritional deficiencies** (including hypovitaminosis and avitaminosis) :

In man, this group includes neuro-anæmia or "subacute combined degeneration" (*see* below): pellagra (pp. 445 and 1076): and lathyrism (p. 1077) ; whilst in certain examples there may be a **combination of deficiency with some toxic factor,** as in ergotism (pp. 168 and 244) or alcoholism (pp. 445, 1051, 1180 and 1184).

(2) **Viral Infections** (*see* Chapter IV, p. 96 *et seq.*) :

These include the series of disorders sometimes known as post-infectious disseminated encephalitis, in which there occur processes of demyelination (some varieties of which are termed "acute perivascular myelinoclasis"), for example those which follow on vaccinia and smallpox (p. 98): measles (p. 118): and, less frequently, chickenpox (p. 104). German measles (p. 119): and possibly influenza (p. 120) (although in the past the term "influenza" has been applied rather indiscriminately—usually by the patients concerned—to almost any form of indefinite febrile attack) : and also the form supervening occasionally after immunisation against rabies (p. 114) : also in Australian X disease (in man, but not when it attacks animals—p. 113) : in equine encephalomyelitis (p. 114) both in man and in animals : and in some other viral diseases such as canine distemper which are confined to certain of the lower animals.

(3) **Toxins** or **poisons** (*see also* under the first heading above) :

In the demyelinating encephalitis associated with **drugs** such as arsphenamine and sulphonilamide (p. 637 and footnote on p. 985). The poisonous action of alcohol or of ergot may act more deleteriously in patients already suffering from vitamin-deficiency or from gastro-intestinal disorders and insufficiency (p. 653), as in the so-called variety of "subacute combined degeneration" associated with alcoholism (p. 1051).

(4) **Unknown ætiology,** including the classical example of demyelinating disease, disseminated sclerosis itself (p. 1059) and the allied condition of "neuromyelitis optica" (p. 1062) and its acute, subacute and chronic forms or variants : together with other rarer disorders.

SUBACUTE COMBINED DEGENERATION of the SPINAL CORD or NEURO-ANÆMIA (*Synonyms :* subacute combined sclerosis, funicular myelosis).

The term "**neuro-anæmia,**" the equivalent of the French "*syndrome neuro-anémique,*" is coming into use and may perhaps replace the other names of this disorder, most of which are in some respects inappropriate. For example, the disease may be acute or very chronic, as well as "*subacute*": the "*combined*" character of its lesions in the cord can be irregular and uncertain: whilst "*sclerosis*" is *not*, at all events until comparatively late in the disease, either a prominent or an important feature of the histological picture. Moreover, a similar combination of dorsi-lateral lesions in the cord is sometimes produced by diseases other than that under discussion. The precise causation of the neuro-anæmic syndrome is still a matter of debate, but **its frequent association with Addisonian or "pernicious" anæmia** makes the supposition practically certain that **both** of these conditions are brought about by some common ætiological factor or factors. **Achlorhydria,** and also **achylia,** are almost invariable accompaniments of both. Other aspects of the problem of the causation of "Addisonian Anæmia" are discussed on p. 647 *et seq.*, and references to the results of the defective functioning of the stomach and liver will be found on pp. 647 *et seq.* and 727–8 respectively.

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[1] This grouping is modified from that given by G. M. Findlay, of the Wellcome Institute of Scientific Research, London, in his paper introducing a "Discussion on Nervous Affections in Man and Animals," *Proc. Roy. Soc. Med.*, 1940, **33,** 162.

FIG. 747. *Subacute combined degeneration of cord*: transverse section of cervical enlargement in a woman, aged fifty-six, with *Addisonian anæmia,* showing patchy, but more or less symmetrical, *demyelination* of the dorsal columns: and of the postero-external aspects of the lateral columns into which the degeneration is, in this particular case, spreading from the surface, over which there is thickening of the membranes. The patient had suffered for two years from difficulty in walking. (Weigert-Pal method for myelin.) × 9.

Neuro-anæmia, like Addisonian anæmia itself, attacks both sexes equally, particularly individuals between the ages of fifty and sixty; and, in several series of cases recorded by different writers, the case-incidence of subacute combined degeneration has varied from 5 up to as many as 80 per cent. of the Addisonian patients under observation. Though this particular form of anæmia is the one with which these spinal-cord lesions have been associated most frequently, they are sometimes found also in, or along with, other types of anæmia, both macrocytic and microcytic. Not infrequently, moreover, "subacute combined degeneration" occurs apparently independently of, or at all events prior to, the development of the anæmia.

The disease is a **demyelinating degeneration** which involves especially the

dorsal and **lateral columns of the cord,** with maximum incidence in the thoracic, and a variable degree of spread upwards into the cervical, regions. In some instances, the degenerative changes have been traced as high even as the nerve-fibres in the internal capsule, and they may spread downwards into the upper lumbar region. The degeneration and demyelination tend to affect especially the **longer** nerve-fibres, those most liable to attack being (1) the ascending fibres of the dorsal columns, with the production of **ataxic symptoms** resembling those of tabes dorsalis (p. 1016 *et seq.*) : and (2) the descending fibres of the lateral cortico-spinal or crossed pyramidal tracts in the lateral columns (Figs. 747 and 748–9 (A)), leading to the development of **spastic paraplegia,** and perhaps later to **flaccid paralysis** if the lower neurones become involved. Along with these clinical phenomena resulting from the degeneration, there is also **loss of deep reflexes.** All varieties and variations in the severity, extent and distribution of the lesions in these two regions, *i.e.*, the dorsal and lateral columns of the cord, occur in individual examples ; and a reference to Figs. 747 and 748–9 will explain why in one patient **ataxic,** in another **paraplegic,** symptoms predominate. The earliest lesions, as may be seen in the lateral columns in Figs. 748 and 749 (A), are small, focal and scattered, and with indefinite margins, rather than systematic or funicular in distribution ; and, by the general extension and fusion of these smaller patches, larger areas of degeneration, affecting both axis-cylinders and myelin-sheaths, then tend to be formed, until, in extreme cases, practically the whole of the white matter of the cord becomes involved—with the exception of a zone of the shorter intrinsic association-fibres immediately around the horns and commissure of the grey matter, a phenomenon well illustrated in the dorsal columns in the various sections in Fig. 748. In these sections is also shown the tendency of the lesion to affect especially the upper thoracic and lower cervical regions, and hence to be most advanced in those parts of the cord. As in syphilitic tabes dorsalis, the lesions tend to be bilaterally symmetrical, but, unlike the process of wasting and narrowing of the dorsal columns characteristic of that disease (*see* first footnote on p. 1016), the affected portions of the cord in neuro-anæmia are, especially in the early stages, often swollen and œdematous, a phenomenon seen particularly in the cervical section in this individual instance. In these illustrations it will also be noticed that the demyelination (now often termed " myelinoclasis ") has *not* to any appreciable degree affected the dorsal nerve-roots (which still show the staining of practically intact myelin-sheaths), although in the more advanced cases of neuro-anæmia a minor degree of degeneration and demyelination may be found in these and also in the corresponding peripheral nerves. The nerve-cells associated with the degenerated fibres are, as a rule, not seriously affected ; and exactly why the axons rather than the cell-bodies of the neurones should be picked out by the degenerative process is still unknown, though the problem is in all likelihood connected with the question of the nutrition of the longer fibres and their sheaths. The changes in the lesions are more of the nature of a patchy necrotic softening and fenestration, than of glial proliferation and sclerosis, though some degree of these chronic processes may ensue later. During the earlier stages of the degenerative process, aggregations of phagocytic foam-cells or " myelophages " similar to those occurring in degenerating or necrosing tumours (Figs. 659 and 660, pp. 1084 and 1085) and in or around inflammatory and hæmorrhagic lesions (Figs. 644 and 645, pp. 1055–6) are found (Fig. 749 (C) opposite), and, as these cells swell and disintegrate, they give place to the loose fenestrated appearance of the so-called " status spongiosus," characteristic especially of the more advanced stages of the degenerative process (Fig. 749 (A) and (B)). There is usually no tendency to any special localisation of the demyelinating process around the vessels, nor is there any perivascular small-round-celled infiltration, *i.e.*, the process does *not* appear to be of an inflammatory nature. Once the lesions have become established in the cord, the change is not a "reversible " one, *i.e.*, there is little or no possibility of, or attempt at, repair Hence treatment must be aimed at prevention rather than cure, because, in thoroughly treated cases of Addisonian anæmia, degenerative changes in the cord, if not already present, are less likely to supervene as long as adequate treatment is perseveringly carried out. On the other hand, it is believed by some that the incidence of involvement of the nervous system has actually increased of late years because of the larger numbers of patients with Addisonian anæmia who survive owing to their having been kept alive by liver-therapy and other modern methods of treatment—including making good the deficiency of hydrochloric acid and pepsin in the gastric juice, and also, as advocated by Mellanby (pp. 439, 444, 1016, 1077), the administration of vitamin A, as well as of vitamin B.

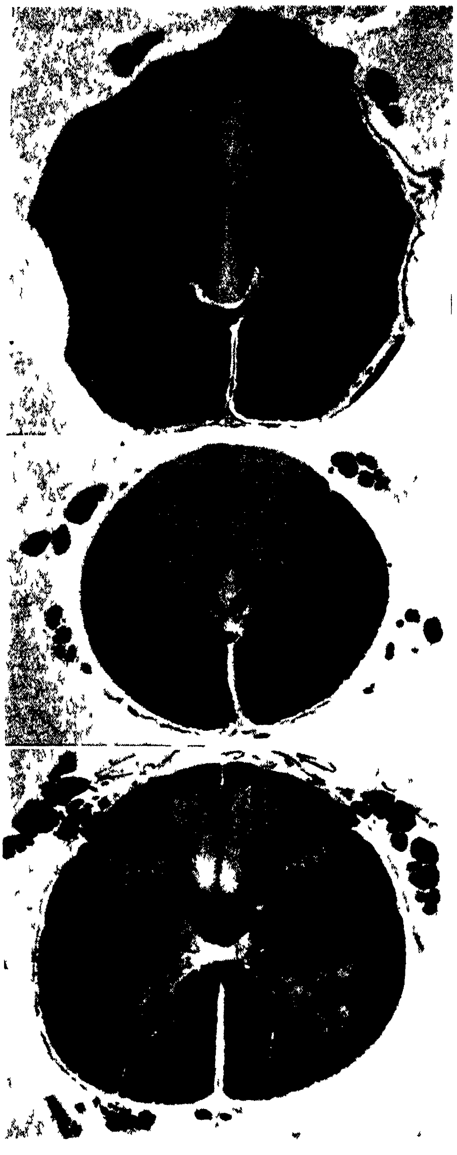
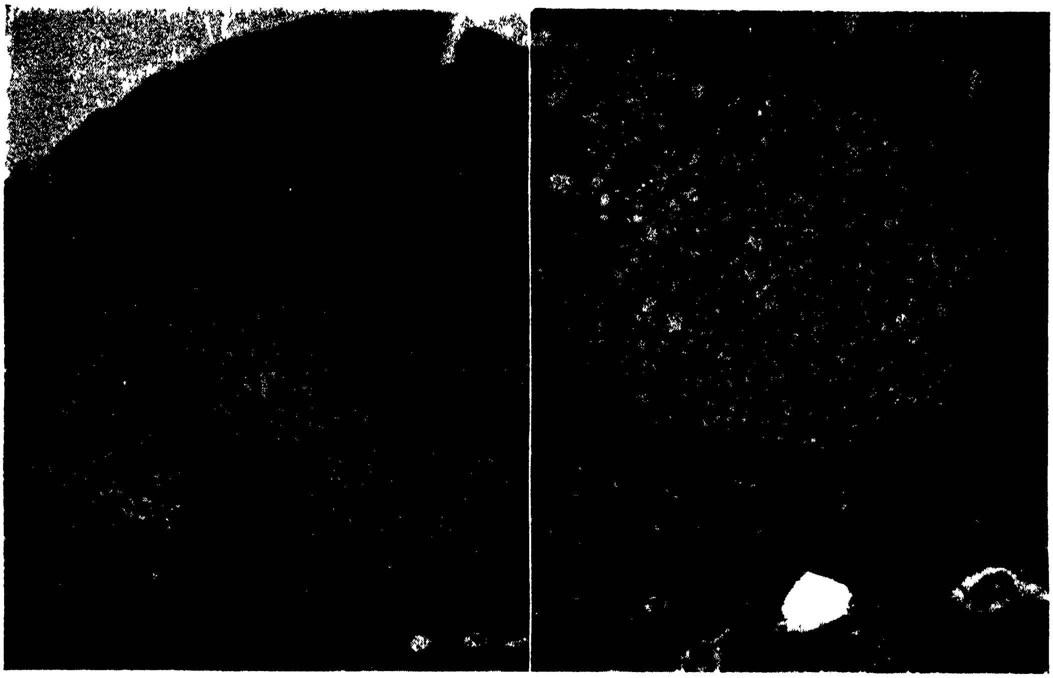


FIG. 748. " *Subacute combined degeneration* " *of the spinal cord associated with Addisonian anæmia* transverse sections in the cervical, thoracic and lumbar regions of the cord, from another female patient also aged fifty-six, in whom the demyelination is well advanced in the dorsal columns, simulating the appearances seen in a case of tabes dorsalis; whilst, in the lateral columns, there is only slight commencing demyelination in the thoracic and cervical regions, but none visible in that position in the lumbar section. Note the swelling and softening (*not* " sclerosis ") in the cervical region, and compare with the illustrations, in Fig. 749 opposite, for details of the degenerative process in the thoracic region. (Weigert-Pal method for myelin.) × 5½.

The motor and other nerve-cells of the grey matter of the cord and the cells of the dorsal-root ganglia may show minor consecutive changes due to interference with their axons, and similar degenerative phenomena have been

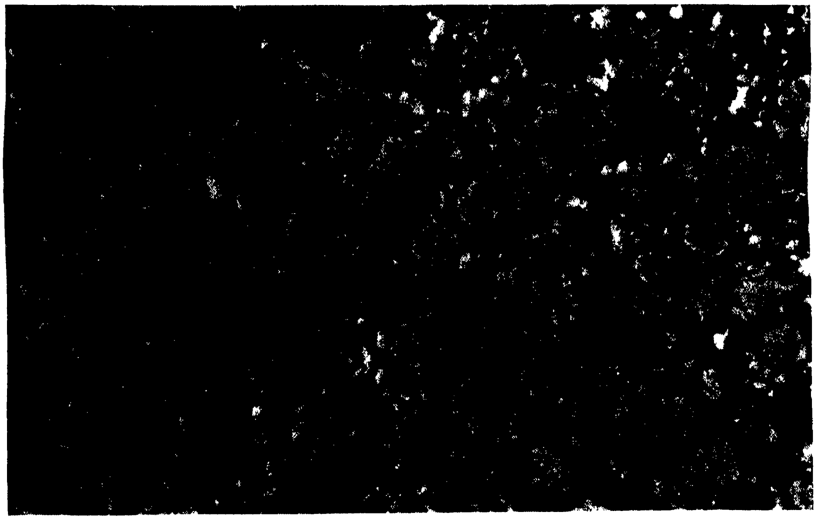


(A) × 30.

(A) Very low-power view to show the lesion, advanced in the *dorsal*, but still comparatively early in the adjoining part of the *lateral*, *column*—in the thoracic region of the cord (*see* Fig. 748 opposite).

(B) × 90.

(B) Ordinary low-power view of central anterior or ventral portion of the *dorsal columns* showing the softening and active phagocytosis of myelin by " foam-cells " in the demyelinated area. The central canal is seen towards the lower margin.



(C) × 400.

(C) High-power view showing the "*foam-cells* " or " *myelophages* " laden with the fatty debris of the disintegrating myelin-sheaths of the degenerated fibres in the affected area illustrated in (A) and (B). Compare with the so-called " *xanthomatous reaction* " in tumours (Figs. 659 and 660, pp. 1084–5 : and *cf.* also the so-called "*xanthosarcoma,*" p. 1228) : and in inflammatory lesions (Figs. 644–5, pp. 1055–6).

Fig. 749. *Subacute combined degeneration of the spinal cord.*
Hæmatoxylin and eosin. (W.E.H. case.)

described in the cortical pyramidal cells. According as the ascending sensory tracts of the dorsal columns or the descending motor cortico-spinal or crossed pyramidal tracts of the lateral columns are affected, so will the histological lesions in them vary at the same and at different levels of the cord, the maximum changes being located, as already noted, usually in the thoracic region. As stated above (p. 1160), little or no regeneration of these tracts in the cord itself seems to take place as the result of liver-therapy and other forms of treatment, and any clinical improvement noted in some patients is probably the result of the degree of healing or regeneration still possible in any of the less seriously affected peripheral nerves. In the cord itself, as compared with the shorter internuncial and other fibres, the longest fibres, as already stated, suffer most, and hence the name " funicular myelosis " sometimes applied to the disorder, a term, however, for the reasons already indicated, not entirely appropriate. In the earlier stages of the disease, the softened and swollen portions of the cord have a greyish translucent appearance on section ; but, in old-standing cases, the degenerated spongy tissues may undergo some degree of shrinkage and become firmer in consistence. As in many other degenerative conditions of the cord, corpora amylacea are common.

In addition to the clinical examination of the **blood** and **gastric contents** in these cases, the investigation of the **cerebrospinal fluid** is important, its characters being mostly negative, in contrast with the various positive findings in syphilitic tabes, disseminated sclerosis and—though in a lesser degree—in multiple neuritis. In neuro-anæmia, there is usually only a moderate increase in coagulable protein, with a trace of globulin, and sometimes a slight increase in the number of cells—perhaps to 5 or 10 small lymphocyte-like cells per c.mm. The colloidal-gold curve, as a rule, shows little change from normal.

In Addisonian anæmia, apart from its association with these degenerative lesions in the spinal cord, the presence of multiple patches of demyelination in the white matter of the brain has been described as of very occasional occurrence (Sjovall, Helsinke, 1937, quoted by Findlay).[1]

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[1] *Loc. cit.*, p. 164.

SECTION XIV

DISEASES OF THE SPINAL CORD AND ITS MEMBRANES

Normally, the **cerebrospinal subarachnoid space** with its basal cisterns, the ventricles of the brain and the spinal theca, and—theoretically, at all events—the **central canal of the cord,** form a continuous system of spaces containing the cerebrospinal fluid (p. 957). The central canal of the cord, however, presents considerable variations. Typically, and early in life, it is a narrow slit-like channel communicating above with the cavity of the fourth ventricle : closed below : and lined by cylindrical or cubical ependymal epithelium, supported externally by a condensed layer of neuroglia. In a considerable number of otherwise "normal" cords, and especially as age advances, the canal is found to be minimal in size or partially or even entirely obliterated, and represented, in many transverse sections, merely by a small solid clump of ependymal cells. Even when the lumen is still present, it is common to find small "ectopic" groups of ependymal cells amongst the glia in the immediate neighbourhood, and it is not improbable that these may, in certain circumstances, be the site of proliferative abnormalities and occasionally of neoplastic growths such as ependymoma or other form of glioma (Figs. 707 and 708, pp. 1119–1120).

Under pathological conditions, the **canal** itself may be **dilated** ; whilst its **obliteration,** as just noted, is of such frequent occurrence as to be regarded almost as a "normal" finding. As in the case of the brain, an over-accumulation of cerebrospinal fluid may take place in connection with the spinal cord, either in its theca (p. 965 *et seq.*) or in the central canal, the latter condition being known as **hydromyelia**—not to be confused with syringomyelia (*see* below). Distension of the canal with blood is called **hæmatomyelia,** an uncommon result of trauma or of bleeding into it from other causes.

Cavities are found occasionally in the cord which do not communicate with the central canal, but the walls of which have a structure similar to it, and which probably arise from or in common with the original canal in the process of its development. Again, various **pseudocystic cavities** without ependymal or other definite cellular lining may be formed by areas of softening in connection with tumours, infarcts, hæmorrhages, and degenerative lesions, or sometimes, in the ventral horns, as the result of acute poliomyelitis (p. 109).

CONGENITAL ABNORMALITIES :—

Spina Bifida or **Rachischisis** : one form of "**Status Dysraphicus**" [1], *see* p. 1066 *et seq.*

SYRINGOMYELIA,[2] another form of "Status Dysraphicus," is a congenital, and sometimes familial, maldevelopment or abiotrophy—"an inborn weakness"—of the tissues of the spinal cord, leading, not during childhood itself, but later, *e.g.*, in early middle life, to the production of cavities in its substance, accompanied and followed by surrounding gliosis (Fig. 750, p. 1164). Whether factors such as trauma and hæmorrhage, or various infective conditions, are capable of stimulating into activity the degenerative process whereby these cavities are formed in areas of pre-existing and inherent congenital weakness, is a much debated problem upon which we ourselves have no direct evidence to offer. In its sex-incidence, syringomyelia is found in males oftener than in females in the ratio of about three to one ; and the first appearance of clinical evidence of its presence is commonest between the ages of twenty or twenty-five and forty years. It may occur alone and as the outstanding feature in individual cases ; but, in an as yet unascertained proportion of instances, it has been found as part of certain more general congenital syndromes (p. 1130), such as multiple neurofibromatosis [1] (p. 1135), tuberous sclerosis (p. 1134), and also, it is said, occasionally in acromegaly (p. 811), as well as being associated with congenital deformities such as spina bifida (p. 1066), or the presence of an accessory cervical rib (p. 1201).

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[1] "Dysraphicus," from ῥαφή, *rhaphē*, a seam or suture, from ῥάπτειν, *rhaptein*, to sew or stitch together. Hence dys-rhaphicus = badly united.

[2] "Syringomyelia," from σῦριγξ, σῦριγγος, *syrinx*, *syringos*, a hollow pipe or tube.

The process of formation of the syringomyelic lesion is **non-inflammatory** and **progressively degenerative** in nature, and is characterised by the development in the spinal cord of a cavity or series of cavities not, in ordinary circumstances, derived from the central canal itself. The cavitation affects most frequently the cervical or cervico-thoracic region of the cord, which may be considerably enlarged, broadened and flattened. It occasionally extends up into the medulla as **syringobulbia,** in rare instances even into the pons. In exceptional circumstances, it has been found throughout the whole length of the cord. Preceding the formation of the actual cavity, oftenest in the grey matter of the base of one of the dorsal horns or in the grey commissure posterior or just postero-lateral to the central canal, a homogeneous-looking area of softened and breaking-down glia appears, in which there is progressive degeneration, with the appearance of phagocytic foam-cells (in this connection sometimes called " myelophages "—*cf.* the analogous cells seen in subacute combined degeneration of the cord illustrated in Fig. 749, p. 1161), taking up the debris of myelin and other breaking-down tissue. In this area of softening, there accumulates a yellowish or sometimes blood-stained fluid, which becomes gradually clearer as the cavity develops. The walls of this pseudocyst are at first soft and

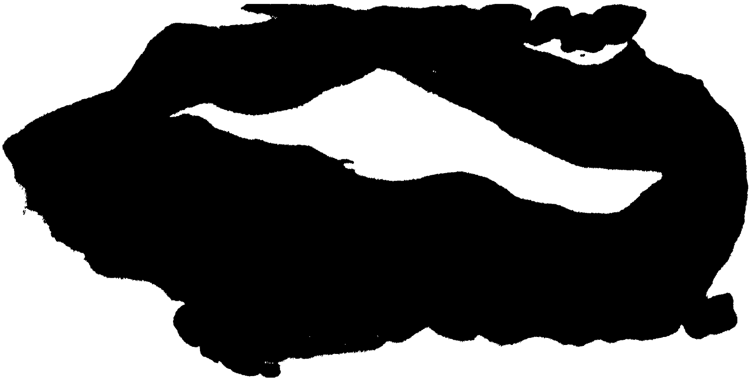

FIG. 750. *Syringomyelia :* transverse section of *cervical cord* showing a large cavity (which in this case involved also the thoracic, but not the lumbar, regions). There is great distortion of the cord, with patchy demyelination and gliosis from compression. (By courtesy of Dr. W. Blackwood.) (Weigert-Pal method for myelin.) × 7.

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[1] " Multiple Meningeal and Perineural Tumours with Analogous Changes in the Glia and Ependyma (Neurofibroblastomatosis) with Report of Two Cases," by Worster-Drought, Carnegie Dickson and McMenemey, *Brain,* 1937, **60,** 85–117. In this paper the bearing of some of the facts elicited by recent experimental work in Inductive Embryology upon the general problem of the causation of these multiple neoplastic and allied syndromes, especially those of congenital origin, is discussed.

gelatinous, but later, from the occurrence of progressive gliosis in and around them, they become firmer and more definite in outline. Where there is a typical well-developed syringomyelic cavity in, say, the lower cervical region, and, if areas at other levels of the cord are examined, it is not unlikely that earlier stages of cavity-formation, or perhaps the patches from which they are developed, will be discovered, the latter showing the more homogeneous phases of the lesion with as yet no breaking-down of the tissues, or, it may be, already progressing to the earlier or the intermediate stages of disintegration (Fig. 707, p. 1119). The size, shape and position of the cavity or cavities in syringomyelia are, therefore, highly irregular and vary from a small space with softened walls, just beginning to form, up to a large distended cavity like that in the illustration (Fig. 750 opposite), occupying much of the transverse section of the cord and causing extensive compression and destruction of the neighbouring tissues of the cord itself. Involvement of the conducting fibres concerned with the sensation of pain and temperature, but with the sparing of those concerned in touch and postural sense, tend to produce the anæsthesia-dissociation picture clinically characteristic of syringomyelia, *i.e.*, the presence of the isolated phenomena of analgesia and thermo-anæsthesia. Secondary involvement of the dorsal columns and nerve-roots, cortico-spinal tracts, ventral-horn cells and ventral roots, leads to the production of sensory and trophic changes, especially in the upper limbs (in the fingers, for example, as the "painless whitlows"—"*parésie analgésique*"—described by Morvan in 1883 (Fig. 798, p. 1240)—changes in bones and joints ("arthropathies," especially of the shoulder and elbow): together with progressive spastic and atrophic paralyses of muscles.

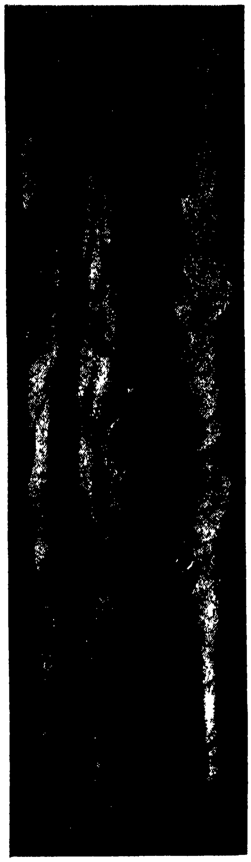

FIG. 751. *Large thin calcified plaques in the leptomeninges of the cord* from the case of a woman aged fifty-five years, who during life showed no symptoms to suggest their presence. Two-thirds natural size.

Calcareous Degeneration occurs in the form of thin pearly-white plates, often showing concentric lamination, and possessing sinuous or irregular edges continuous with the membrane in which they occur. They are found, most frequently, in the pia-arachnoid of the cord or nerve-roots, and generally give rise to no symptoms during life (Fig. 751 : and *cf.* pp. 971 and 1093).

Injuries and Accidents to the Cord [1] in civil life are rare, except in cases of fracture or dislocation of the spine, for example of its upper part in hanging, or in motoring and other accidents, and in gunshot and other wounds, in which lesions the tissue of the cord may be lacerated, crushed, or even torn across In a review of cases of injury to the vertebræ occurring in the Royal Air Force [1] for the five-year period previous to 1940, of fifty-seven such cases nine were due to flying accidents, of which seven were caused by accidents to aircraft. In all of these seven, there was fracture of the **bodies** of the vertebræ, but in only one of them was there serious damage to the cord (recorded as " physiological transection " with death seven months after the accident). In the same series of cases, *non*-flying accidents, such as might equally well have occurred in civil life (cycling, motoring, falls, etc.), also numbered nine (five being compound fractures), and in only one of these was there serious injury to the cord leading to the patient being invalided out of the service.

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[1] In connection with these, *see also* p. 1026.

Concussion of the cord, *e.g.*, in railway and other accidents ("railway-spine," " traumatic neurasthenia," etc.) may produce symptoms of all degrees, depending upon the severity of the concussion, which is often not merely of the cord but also, and perhaps chiefly, of the brain. In many cases, allowance must be made for the psychological factor, and it is not an unknown occurrence for recovery to be rapid *after* a successful action for damages. In other instances in which the concussion has been severe, petechial hæmorrhages and varying degrees of degeneration, with paresis or paralysis of limbs, etc., may result. (*See also* p. 1026.)

Hæmorrhages of any great size into the substance of the cord, apart from those due to injury, are uncommon. **Petechial hæmorrhages,** as just stated, may occur as a result of severe concussion and are frequently found around an area of acute softening—and these or larger hæmorrhages are found in shell-shock, scurvy, cerebrospinal meningitis, and analogous conditions. Hæmorrhage into or on the surface of the meninges is found as a direct spread from above in cases of intracranial hæmorrhage (p. 1035 *et seq.*). Hæmorrhage into the central canal is known as **hæmatomyelia** (p. 1163), and is rare.

INFLAMMATION OF THE SPINAL MENINGES [2] :—

(*a*) **Of the Dura-Mater.** (*See* p. 991, where a reference to so-called " **pachymeningitis hypertrophica** " will also be found.)

(*b*) **Of the Leptomeninges.** (*See* p. 991, and *cf.* pp. 979 to 990.)

The findings in the **cerebrospinal fluid** in the various forms of leptomeningitis are described on p. 958 *et seq.*: meningococcal on p. 984 : tuberculous on p. 993 : acute lymphocytic choriomeningitis on p. 1001 : and syphilitic in its various forms on pp. 1009, 1016 and 1019.

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[1] By Wing Commander Philip A. Hall and Flight Lieutenant George H. Morley, *Brit. Med. Jour.*, 1940, i, 159. Numerous references to the literature of the subject are given.

[2] Spinal meningitis, as it occurs, as a rule, in conjunction with inflammation of the cerebral meninges, is described on p. 991.

INFLAMMATION OF THE SPINAL CORD (MYELITIS):—

The terms "**myelitis**" and "**myelomalacia**" are frequently applied, more or less indiscriminately, to any **softening** of the spinal cord. The former term is often inaccurately employed in this connection, as, in many instances, the condition is not a true inflammation, but is due to injury or compression, or to mechanical interference with the blood- and lymph-supply.

Inflammatory softening of the cord, *i.e.*, **myelitis proper,** results from the action of micro-organisms and their toxins. It occurs either in irregular patches, or along the lines of the nerve-tracts. It is sometimes a complication or sequel of acute infective diseases such as typhoid fever, influenza, pneumonia or dysentery, the infection taking place especially by way of the blood-stream. It is said sometimes also to result from "cold and chill," but these must be regarded merely as predisposing causes. Similarly, alcoholic subjects especially are said to be liable to myelitis. **Syphilis,** quite apart from the formation of gummata, is one of the commonest causes of myelitis, which in some cases supervenes comparatively early in the course of the infection, but is of more frequent occurrence in the later stages of the disease (pp. 1008–9). It is, as a rule, associated with vascular and meningitic lesions, *i.e.*, in the form of syphilitic meningo-myelitis (Figs. 605–8, pp. 1006–8) ; and is found mainly in the thoracic region of the cord.

Non-inflammatory softening, or **myelomalacia,** may follow injuries to the cord, pressure upon it by prolapsed intervertebral cartilages (pp. 1026 and 1220–23), or by tumours, tuberculous masses or abscesses, or by syphilitic gummata or meningitis. Infiltration of its substance by these processes, if themselves infective, will lead to a combination of compression-myelomalacia and true myelitis. Myelomalacia occasionally follows the injection of certain radio-opaque substances into the spinal theca (*cf.* p. 1059).

Softening of the cord results also from **vascular obstruction,** whether produced by pressure on the vessels from without, or by embolism, or by thrombosis in degenerated, often syphilitic, vessels (*see under* Infarction, p. 178).

Distribution and Characters of the Lesions. These may be transverse, diffuse, or patchy and disseminated. A "**transverse myelitis,**" so-called, is perhaps more frequently of the nature of a myelomalacia than a true inflammatory lesion, though in some instances, as indicated above, both of these factors play a part in its production. It affects only a limited length of cord, perhaps one or two segments, but tends to involve both the white and the grey matter across the entire thickness of the cord. A complete transverse lesion of this nature may be the result of direct injury in fractures or dislocations, or of compression of the cord ; or it may be due to vascular obstruction ; but in some cases the exact nature of the cause remains obscure. **Diffuse myelitis** is liable to occur in some of the acute infective and infectious diseases ; whilst the **disseminated** or **scattered form** occurs in multiple foci, most usually in certain of the viral infections, the resulting demyelination tending sometimes to attack the nerve-fibres immediately around the blood-vessels and thus giving, in sections stained for myelin, a highly characteristic histological picture. When such infections attack the **grey matter** of the cord, the resulting lesion is termed a **poliomyelitis** (*see* footnote, p. 1049). For a description of acute anterior poliomyelitis (infantile paralysis) *see* Chapter IV on "Viral Infections," p. 105 and section on Acute Anterior Poliomyelitis and Polioencephalitis on p. 1049.

On naked-eye examination, there is usually a varying degree of engorgement of the vessels of the pia, mainly over the affected portion of cord, which is intensely congested and much softened—sometimes diffluent or semi-diffluent. Numerous minute hæmorrhages may be present, and in some cases there is a moderate degree of lepto-meningitis.

On transverse section, the normal markings and the differentiation of the component parts of the cord are obscured and often completely lost. In the later stages of the forms due to continued pressure, the congestion subsides, and the creamy softening, becoming more pronounced, spreads both up and down the cord.

On microscopical examination, the blood-vessels are seen to be distended, and round them, in the perivascular spaces, are accumulations of leucocytes, mainly of lymphocytic type ; but polymorphonuclear leucocytes and plasma-cells may be present. Granular masses of blood-pigment are sometimes found in the neighbourhood of the vessels. The neuroglia-cells are swollen, vacuolated, and frequently multinuclear, and, if the process is slowly developed, the neuroglia itself undergoes proliferation and the nerve-tissue elements are relatively diminished. On transverse section, the nerve-fibres are seen to present great variations in their diameter, some swollen, others atrophied. The axis-cylinders may be enlarged and beaded, and, later, undergo fragmentation and ultimately disappear. The myelin-sheaths become distended and the myelin thinned, or broken-up and granular. The nerve-cells in the grey matter show varying degrees of degenerative change. They become swollen and rounded in outline, the nucleus eccentric and staining less intensely, and there is perinuclear, or perhaps complete, disappearance of the Nissl-granules. The cytoplasmic processes also show various stages of degeneration, from slight alterations in structure up to complete disappearance. Areas of secondary degeneration are seen extending for a varying distance both above and below the seat of the lesion. The whole affected portion of the cord often becomes infiltrated with leucocytes and degenerated neuroglial cells, and especially with microglial foam-cells, compound granular corpuscles or " myelophages," actively engaged as phagocytes in removing the degenerated and disintegrating myelin (*cf.* Fig. 749 (C), p. 1161) and other debris.

In extreme cases, film-preparations show fat-droplets, compound granular cells, leucocytes, degenerated and vacuolated nerve-cells, granular detritus, and, sometimes, bacteria.

When the lesion is brought about by gradually increasing pressure, the changes are less acute, and the grey matter suffers in less degree than the white.

Ascending and descending degenerations in the implicated spinal nerve-tracts, paralysis and wasting of muscles, bed-sores, cystitis and pyelitis and perhaps involvement of the kidneys from paresis and infection of the bladder, are usual accompaniments of myelitis. In other instances, suppurative infection of the vertebral canal and its contents results from the erosion into it of bed-sores, and these two conditions—acute decubitus and myelitis—thus tend to aggravate one another.

If the patient survives the more acute stages of the attack, the condition frequently becomes **chronic**; the myelin, granular cells and debris are absorbed; and a so-called **grey softening** results. In this stage, there is progressive proliferation of the neuroglial tissue—**sclerosis**—and the nerve-fibres and the nerve-cells to a large extent disappear. The neuroglial tissue at first appears looser and more open and spongy in texture. Contraction and condensation take place later, and, eventually, the softened area is replaced by a cicatrix or occasionally by a pseudocystic cavity, and the motor and sensory conduction in the affected region of the cord is interrupted.

DEGENERATIVE CONDITIONS OF THE SPINAL CORD

In this group are included a series of diseases characterised by varying degrees of destruction of certain **conducting tracts** and **groups of nerve-cells** in the spinal cord, in which the processes bringing about the pathological changes appear to be **degenerative** rather than inflammatory, though in some there may have been the occurrence of a preliminary, or perhaps antecedent, acute disease. The causes of many of these lesions are still unknown. Some are undoubtedly the result of certain conditions of **deficiency,** for example, the inadequate intake or deficient absorption of vitamins, particularly of the A and B groups (pp. 439–40 and 444–5) : or the defective secretion of digestive ferments, hæmopoietic and analogous " factors " (p. 647 *et seq.*), or the hormones of ductless glands : or combinations of these, perhaps in some cases along with the harmful action of some **pathogenic micro-organism,** particularly the spirochæte of syphilis. As suggested in the section dealing with tabes dorsalis (p. 1016), it is now regarded as probable that the nervous tissues of certain **syphilitic** patients are rendered more vulnerable to the attack of the spirochæte when they are already weakened by **some deficiency in the supply of vitamins** needful for the nutrition of the central nervous system and its maintenance in health. The degenerative processes in the neuraxis may be limited to one particular tract, or to one group or column of nerve-cells; but, very commonly, combinations take place, two or more tracts possessing different functions, or certain conducting-tracts and certain groups of nerve-cells, being involved. The resulting degenerations may be **ascending** or **descending,** according as sensory, motor, or communicating tracts are affected.

MOTOR-NEURONE DISEASE. Of this disorder or, perhaps more accurately, group of disorders, two forms, each previously regarded as a distinct clinico-pathological entity—the "**progressive muscular atrophy**" described about the middle of last century by Duchenne (1847–53) and Aran (1850) and the "**amyotrophic lateral sclerosis**" of Charcot (1869)—together with the intermediate form known as "**bulbar paralysis**"—are now by most authorities grouped together under the general term "**motor-neurone disease,**" the clinical symptom-complex of these depending rather upon the anatomical situation of the particular motor neurones involved than upon any ascertainable difference in the nature of the lesion. If the **nerve-cells** first attacked are those of the **ventral horns** of the spinal cord, that is to say, the cell-bodies of the lower motor neurones, for example (as is most commonly the case) those of the cervical enlargement, the clinical picture is that of **progressive spinal muscular atrophy,** the effects of which tend to show first in the small muscles of the hand, with wasting of the thenar and hypothenar eminences, spreading progressively, as the name implies, to the muscles of the forearm, upper arm and shoulder-girdle and then to the body and lower limbs. Occasionally, the process commences in the lumbar enlargement. Both sides are usually affected, though not in every case necessarily symmetrically. Scattered single cells are first picked out, the corresponding groups of muscle-fibres which these supply undergo degeneration, progressive atrophy and disappearance, whilst the intervening and still surviving fibres exhibit the characteristic twitching or fibrillation indicating early irritative changes in the remaining motor cells. Increasing numbers of the cells in the ventral horns become affected, and the process tends to spread downwards through the thoracic region of the cord to the lumbar enlargement, producing atrophy of the corresponding muscles. It may also spread upwards to involve the upper cervical motor cells and the analogous cells of cranial motor nerve-centres in the medulla oblongata.

FIG. 752. *Progressive muscular atrophy* in an elderly male, showing the wasting of the small muscles of the hand. (W.E.H. case.)

In some instances, the process begins, not in the spinal cord, but in the motor nuclei of the hypoglossal, vagus and glosso-pharyngeal cranial nerves, and is then known as "**bulbar paralysis,**" affecting the tongue, pharynx and œsophagus; and, when the motor root of the seventh cranial nerve in turn becomes attacked, the paresis or paralysis and atrophy spread to the lips and other facial muscles. The nucleus of the motor root of the trigeminal (and, though less frequently, the nuclei of the nerves to the muscles which move the eyeball) may also come to be affected, if the patient does not succumb to the results, direct or indirect, of some of the foregoing paralytic lesions, which are of lower-neurone type analogous to those already described in connection with the spinal cord.

When the disease attacks the upper, as well as the lower, motor neurones, it in some instances predominates in the former, in others in the latter, set of nerve-cells and their fibres. The lesions often vary in intensity at different levels and produce in the affected cells all the usual evidences of degeneration, viz. : chromatolysis of the Nissl-bodies, eccentricity of the nucleus, vacuolation, and, finally, breaking up and disappearance of progressively greater numbers of cells. Degeneration of the nerve-fibres belonging to these cells and dependent upon them for their nutritive influences, follows, and is found, therefore, in the descending cortico-spinal tracts, *i.e.*, the crossed pyramidal tracts in the lateral columns (hence the term "amyotrophic **lateral** sclerosis") being usually more affected than the direct motor fibres in the ventral columns. The degenerative changes in the upper motor neurones can in many instances be detected also in the cerebral peduncles, internal capsules and motor cortex, with degeneration and atrophy of the Betz-cells in the precentral gyrus, these cells being the neuronal bodies of the upper cortico-spinal elements of the motor system. Degeneration of the middle third of the corpus callosum is also sometimes found. In certain instances, for some reason not understood, there is evidence also of degeneration in the dorsal columns of the cord, more particularly in the dorso-median column of Goll, and also in the rubro-, vestibulo- and tecto-spinal tracts in the anterior columns.

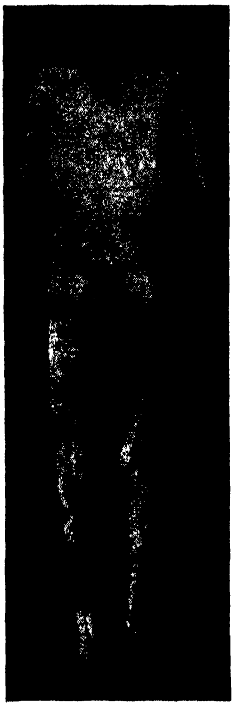
FIG. 753. *Progressive muscular atrophy*, showing advanced wasting in a middle-aged male (a case of the late Professor Greenfield).

A moderate degree of glial proliferation in the affected tracts follows upon the degeneration of the nerve-fibres ; and the ventral nerve-roots and the peripheral motor nerves derived from them show atrophic thinning, and there is also some shrinkage of the grey matter of the ventral horns. Progressive atrophy of the corresponding muscles constitutes the chief clinical evidence of the advancing lesions in the motor neurones. Secondary neuropathic arthropathies or neurotrophic disturbances of joints sometimes supervene in these and similar disorders of the spinal cord (pp. 1239–41).

The disease in its various forms attacks individuals chiefly in early middle life, males more frequently than females ; and, as a rule, it slowly progresses to a fatal termination in some two or three years. Microscopically, there is no evidence that the process is inflammatory, and we therefore prefer not to employ the term "chronic anterior poliomyelitis" sometimes given to it. As indicated in the preliminary paragraph on p. 1169, the ætiology of the disease is unknown, but of late there has been a tendency to suspect the influence of some vitamin-deficiency, and patients suffering from motor-neurone disease, as well as from other obscure degenerative disorders of the neuraxis, have been reported as having shown, at all events partial, arrest of these processes if treated sufficiently early, though, as might be expected from the nature of the lesions involved, damage already done to the neurones themselves cannot be made good by any form of treatment.

Progressive spinal muscular atrophy of infants[1] **(Werdnig-Hoffmann paralysis,** described by them in 1891 and 1893 respectively) and the closely allied (and by some writers regarded as identical) condition of **Amyotonia congenita,** described by Oppenheim in 1900, are disorders manifesting at or soon after birth—in the former, usually familial and progressing to a fatal termination at or before the age of four or five years; whilst in the case of the latter, the familial incidence and grave prognosis have not been characteristic. In both forms, there has been pronounced diminution in the number of the **motor cells of the ventral horns,** with shrinking and varying degrees of degeneration of the cells which survive. Corresponding simple secondary **atrophy of the muscles** takes place, commencing usually with those of the shoulder-girdle and neck or of the pelvic region and then spreading from the muscles of the trunk (the diaphragm remaining unaffected) centrifugally to the limbs, in which, unlike the process in the progressive muscular atrophy in the adult (p. 1170), the muscles of the hands and fingers are the last to be affected. Except for the hypoglossal nuclei in the medulla, the nuclei of the cranial nerves are usually unaffected. The muscular tissue is replaced by fat, often, however, with the escape of a few scattered fibres amongst the fat-cells.

Pseudohypertrophic muscular dystrophy is a disease which, in some respects, resembles the disorders of the above motor-neurone group, but, as no definite lesions have been detected in the spinal cord or motor nerves, we describe it under Diseases of Muscle (p. 1243).

PROGRESSIVE NEURAL MUSCULAR ATROPHY, NEURO-SPINAL MUSCULAR ATROPHY or PERONEAL ATROPHY of Charcot-Marie-Tooth (1886). Unlike the group of motor-neurone diseases described in the preceding section, which as far as is known are *not* hereditary or familial, there are other less common forms of neuro-muscular disease such as that known as "**peroneal atrophy,**" which *are* definitely **heredo-familial** in incidence, and some examples of which have been traced through as many as nine successive generations. Clinically, the disorder shows first, as a rule, in childhood, or occasionally in adolescence; and is commoner in males than in females in the proportion of 3, 4, or 5 to 1 in different series of cases. In some of these recorded series, the disorder has been transmitted indifferently by either parent; but in others (as in the analogous transmission of hæmophilia described on p. 670), it has been passed on by " healthy " carrier-mothers to their male children only, *i.e.*, it shows all variations in the factors of its inheritance—dominant, simple recessive, and sex-linked recessive.

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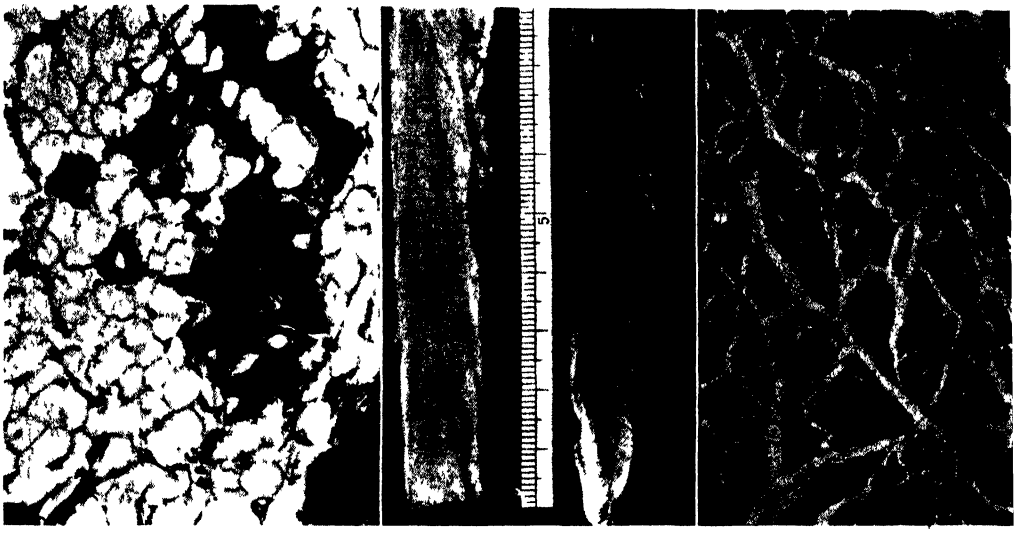
[1] The information in this paragraph is taken from an Edinburgh University M.D. (1928) Thesis by Donald Paterson, who records six cases of the disease, all of them fatal in the first year of life.

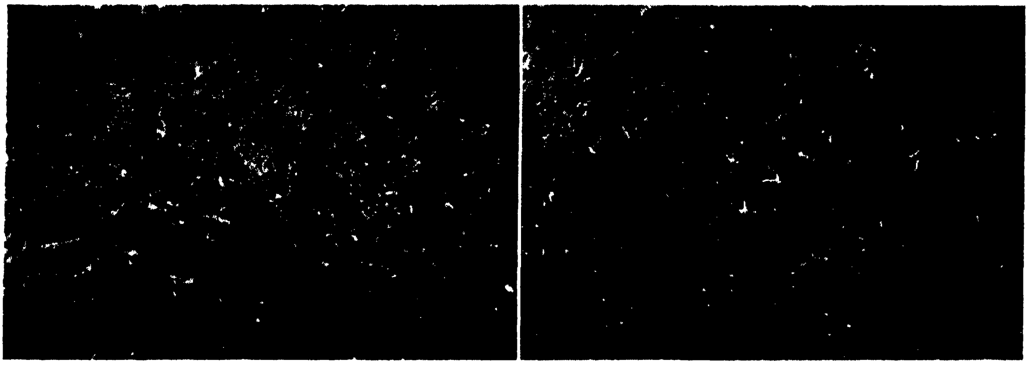
Clinically, peroneal atrophy affects both lower limbs, though not necessarily symmetrically (p. 1247). It commences in the small or intrinsic muscles of the feet, the peroneal muscles and the extensor longus hallucis and other long extensors of the toes; and the paralysis of these muscles leads to the production of pes cavus and a varying degree of club-foot of equino-varus type. The atrophy of the muscles gradually extends up the leg, but may at any stage become arrested, so that the wasting of the lower part of the limb, in contrast with the still comparatively unaffected proximal segment, gives the peculiar and characteristic tapering or "inverted hock-bottle," "stork-leg" or "spindle-shanked" appearance to the limb. As the disease advances, analogous atrophic changes tend to affect the upper limbs, beginning in the small muscles of the hands and then coming slowly to involve the muscles of the forearm. Occasionally, however, the distal parts of *both* the arms and legs are attacked simultaneously.



(a) × 75 (A) (B) (b) × 75

FIG. 754. *Progressive Neuro-Spinal Muscular Atrophy* (or *Congenital Peroneal Atrophy* of Charcot-Marie-Tooth) in an old man of seventy-three, in whom the disorder had commenced clinically at the age of two years, but had not advanced since boyhood, by which time double club-foot and stork-leg had been established. (A) Naked-eye photograph of the pale degenerated *belly of the left peroneus longus muscle* shown in longitudinal section, with (B) a similar section of the adjacent (more or less unaffected) *tibialis anticus muscle* for contrast and comparison (scale in cm. and mm.). (a) A low-power view of a transverse section of the degenerated peroneus longus, showing replacement of the muscle by fibrous tissue and fat—only an occasional isolated muscle-fibre having survived: contrasting with (b) a transverse section of the tibialis anticus, which, for a patient of this age and clinical history, gives a comparatively normal finding as regards both muscle-fibres and their sarcolemma and other supporting connective-tissue structure. (*See also* Fig. 755 on next page.) (Dr. Worster-Drought's case, W.E.H.) (van Gieson and hæmatoxylin.)

Opinion differs as to whether the initial lesion in the motor nerves affects first the end-plates, the nerve-fibres (as a so-called " interstitial neuritis "), or the nerve-cell bodies in the ventral horns—for example at the level of the middle of the lumbar enlargement when the peroneus longus is involved—but it is probable that, ultimately at all events, the *whole* neurone-unit undergoes degeneration, resulting in the secondary degeneration of the corresponding muscles ; and this in turn leads to the characteristic deformities of feet and hands. In addition to the motor-neurone lesions, degenerative changes may be found in the thoracic (dorsal) nucleus of the cord (Clarke's column), present chiefly in the thoracic region, and in fibres of the spino-cerebellar tracts arising from these, as well as in the sensory nerves, dorsal roots and root-ganglia and the afferent fibres from them ascending in the dorsal columns, lesions in these giving rise clinically to various paræsthesias and other sensory as well as trophic disturbances. The disease does not, as a rule, progress to the endangerment of life, and many patients, except for the disability entailed by the deformities and paralysis, survive in good health and may even attain old age. In a case of Dr. Worster-Drought's, investigated by one of the authors, the patient was a man who died of prostatic carcinoma at the age of seventy-three years, the peroneal atrophy having been present since he was two years of age. Fig. 754 from this case shows, in (A), the pallor of the degenerated muscle of the peroneus longus contrasted with the normal appearance of (B) the adjacent and practically healthy tibialis anticus ; whilst sections through the mid-level of the lumbar enlargement (Fig. 755) show almost complete dis-



(C) (D)

FIG. 755. *Progressive neuro-spinal muscular atrophy* (or *congenital peroneal atrophy* of Charcot-Marie-Tooth) : transverse section at the middle of the lumbar enlargement of the cord of the same patient (Fig. 754).

(C) Low-power photograph of the *left ventral horn* showing *entire absence of motor nerve-cells* at this particular level (corresponding to representation of the affected peroneus longus muscle). The whole horn is distinctly shrunken and sclerosed, with thickened vessels and very numerous " amyloid " degeneration-bodies.

(D) A corresponding section of the *right ventral horn* at the same level, showing some degree of sclerosis, but a *moderate number of surviving motor nerve-cells*, exhibiting varying degrees of degeneration. The degenerative changes in the right horn, though present, are, therefore, distinctly less pronounced than on the left side, and only a few amyloid bodies are present. In this connection it is interesting to note that, clinically, the peroneal atrophy, though present in the right leg, was distinctly less complete than on the left side.

(Bielchowsky's silver-impregnation method. × 50.)

appearance of the motor nerve-cells from the ventral horns, some gliosis, and very numerous so-called corpora amylacea.

SECONDARY SCLEROSIS IN SPINAL CORD :—

Secondary degenerations in the cord may be the result of direct injuries to, or of lesions which press upon, the cord itself. Thus, fracture-dislocation of the vertebræ, herniation of the intervertebral cartilages (p. 1220), hyperplastic or fibrotic thickening of the ligamenta flava (p. 1223), aneurysm, syphilitic gummata, or inflammatory exudates may, by pressure upon, or, in the case of some lesions, by direct invasion of the substance of, the cord, be the cause of secondary degenerations. Often, however, the **descending degenerations** are due to interference with the descending tracts or their centres in the brain by hæmorrhage, softening, tumour-formation or other lesions. The main demonstrable change is the destruction of the medullary sheaths, by the process known as **demyelination** or **myelinoclasis.** With the loss of the highly refractile substance of which these are composed, the nerve-fibres appear greyish in colour—**grey degeneration.** Microscopically, in the affected area, there is increase in the neuroglia—**gliosis**—and great reduction in the number, or perhaps complete disappearance, of the axons or nerve-fibres.

As a general rule, the degeneration follows the direction in which the nerve conducts, and therefore **descending degenerations** are found mainly in the [1] :—

1. Lateral and (2) Anterior cortico-spinal (crossed and direct pyramidal) tracts ; but, particularly after transverse lesions of the spinal cord itself, descending degeneration occurs also in the :

3. Vestibulo-spinal tract or ventro-lateral descending tract of Loewenthal, situated at the anterior surface of the cord in front of the ventral horn, and including its bulbo-spinal, ponto-spinal and vestibulo-spinal fibres.

3a. The neighbouring tecto-spinal and olivo-spinal fibres in the bundle of Helweg.

4. Rubro-spinal tract (Monakow's bundle) in the lateral column in front of the lateral cortico-spinal (crossed pyramidal) tract.

5. The descending semilunar or comma-tract lying in the dorsal columns between the (ascending) fasciculus cuneatus and fasciculus gracilis.

5a. The septo-marginal tracts of endogenous fibres lying on each side of the dorsal mesial fissure.

Various other descending short endogenous or communicating fibres. The anterior, lateral and posterior intersegmental fibres along the margins of the grey matter are also affected just below the level of a transverse lesion.

Secondary ascending degeneration, on the other hand, occurs in the dorsal columns, affecting both the :—

7. Dorso-lateral and (6) Dorso-mesial tracts immediately above the lesion, and, at a higher level, the latter only.

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[1] The reader will find it helpful, when following the details given here, to refer, say, to diagram 46 of E. B. Jamieson's " Illustrations of Regional Anatomy," Section I, Central Nervous System, 3rd Edition, 1941 ; or to Figs. 546–7 and 8, in Schafer's " Essentials of Histology," 14th Edition, edited by H. M. Carleton, 1938, pp. 456–7 and 460. The numbers given above in our text are taken from Fig. 546 in the latter book, in which a full description of the course of these tracts and of their degeneration on section will be found (*loc. cit.*, p. 454).

Ascending degenerative changes also supervene in the :—

8. Postero-lateral tract or marginal bundle of Lissauer derived from the in-coming dorsal nerve-roots.

9. Dorsal spino-cerebellar (direct cerebellar) tract of Flechsig, derived from the cells of the thoracic nucleus or nucleus dorsalis (Clarke's column) and therefore present mostly in the thoracic region.

10. Ventro-lateral ascending tract of Gowers, which includes the anterior spino-cerebellar, lateral spino-thalamic, and spino-tectal fibres.

11. Ventral spino-thalamic tract at the surface of the cord opposite the area of emergence of the ventral nerve-root.

12. Ventral sulco-marginal tract of Pierre Marie, lying between the anterior cortico-spinal (direct pyramidal) tracts on each side and the anterior mesial fissure.

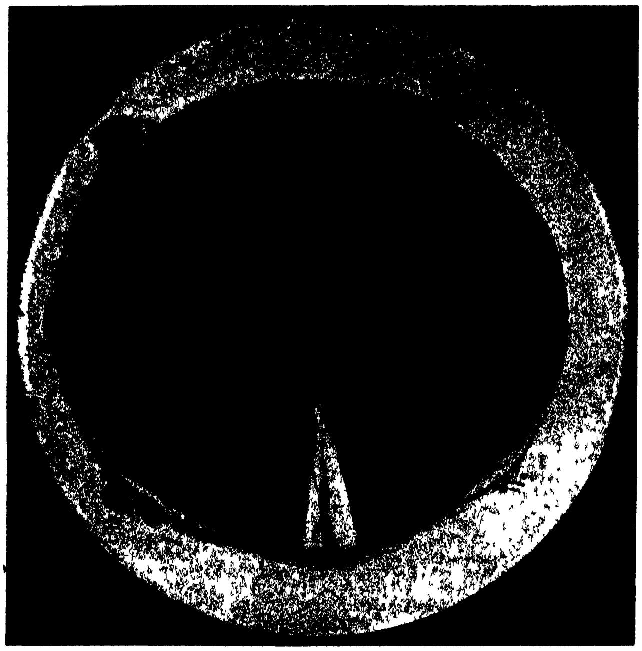

FIG. 756. *Secondary descending degeneration :* transverse section of thoracic region of spinal cord from a case of *hemiplegia*, showing a pale area of demyelination and sclerosis in the lateral cortico-spinal (crossed pyramidal) tract. (The exaggerated width of the ventral fissure is an artifact due to shrinking during preparation, and the white areas are not the ventral cortico-spinal tracts.) (Weigert-Pal method for myelin.) × 6.

These **degenerations, ascending** or **descending** as the case may be, extend through varying lengths of the cord, according to the site and extent of the lesion and the space which the various tracts occupy within the cord.

The commonest form of **secondary descending degeneration** is that which occurs in the cortico-spinal (cerebrospinal or pyramidal) tracts as a result of some lesion in the brain, affecting the motor nerve-cells, or the fibres as they pass downwards from these, *e.g.*, a hæmorrhage into the internal capsule (p. 1040 *et passim*). The degeneration follows the fibres and therefore is seen in the following situations [1] :—

(1) On the **same** side as the cerebral lesion in the :—

(*a*) Middle two-fifths of the basis pedunculi (crus cerebri).

(*b*) Cortico-spinal (pyramidal) bundles between the superficial and deep transverse fibres in the pons, and in the :

(*c*) Anterior pyramid of the medulla.

(*d*) Ventral cortico-spinal (direct pyramidal) tract—the fibres affected in this situation being those which have not yet decussated at the point of observation, or some of which do not decussate.

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[1] *See* Plate 48 of Section I : Central Nervous System (The Motor Path) in E. B. Jamieson's "Illustrations of Regional Anatomy," 3rd Edition, 1941.

(2) On the side **opposite** to that of the cerebral lesion in :—

(*a*) Lateral cortico-spinal (crossed pyramidal) tract.
(*b*) Those fibres of the ventral cortico-spinal (direct pyramidal) tract which have already decussated above the point of observation.

In transverse sections of the cord, **the extent of the area occupied by the degeneration** becomes less as the fibres are traced downwards, because the bulk of both cortico-spinal tracts becomes diminished from above downwards. The degeneration occurs *simultaneously* throughout the whole length of the fibres, and is " descending " only in the sense that it occurs *below* the site of the lesion, the trophic cell-bodies of the neurones being at the upper ends of these in the brain.

If the interference with the descending tracts is in the cord, there is degeneration **below** the lesion, but only to a slight extent above it.

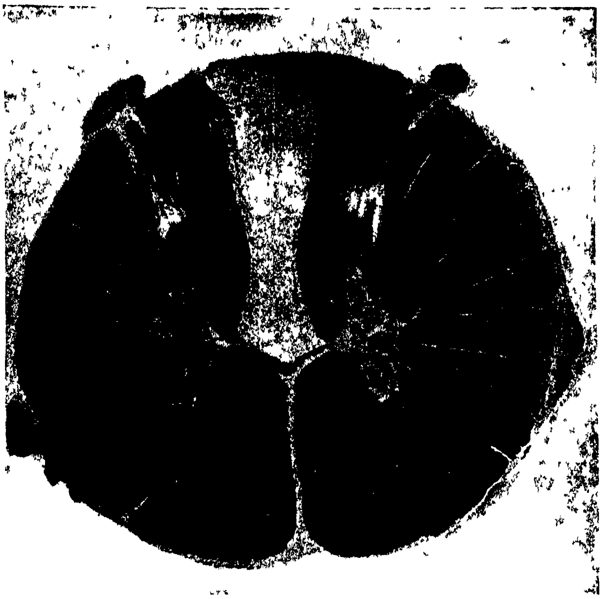

FIG. 757. *Secondary ascending degeneration :* transverse section in thoracic region, with demyelination and sclerosis of the dorso-mesial (postero-internal) tract of Goll on each side, resulting from pressure of a tumour on the lumbar part of the cord. (Weigert-Pal method.) × 6.

Secondary ascending degeneration may occur from pressure on, or injuries to, the cord, or from transverse or other forms of myelitis. When the lesion is in the cord itself, the dorsal columns and the dorsal spino-cerebellar (direct cerebellar) and the ventro-lateral ascending (Gower's) tracts will be affected throughout their whole upward extent in the cord—the other tracts, if they suffer by the injury, only in the more limited regions in which they are situated. Thus, in the lumbar and lower thoracic regions, the whole of the dorsal ascending columns will be degenerated ; but, on passing upwards, the degeneration becomes limited to the dorso-mesial (postero-internal) tracts and the dorsal spino-cerebellar (direct cerebellar) tracts.

SECTION XV

DISEASES OF PERIPHERAL NERVES

If the continuity of a nerve is severed, **degeneration** occurs throughout the entire length of the nerve-fibres of its peripheral portion, which have been thus cut off from their trophic " nerve-cells " or neurone-bodies. The myelin breaks up into droplets and eventually, through the agency of phagocytic cells derived mostly from the proliferated neurolemma-cells, is absorbed ; and the degenerated axons or axis-cylinders, together with their end-organs (motor nerve-plates, etc.), also undergo degeneration and perhaps break up and disintegrate. In addition to these peripheral changes, certain minor grades of degeneration are found to occur in the central portion of the nerve, extending up to and affecting the neurone-body itself.

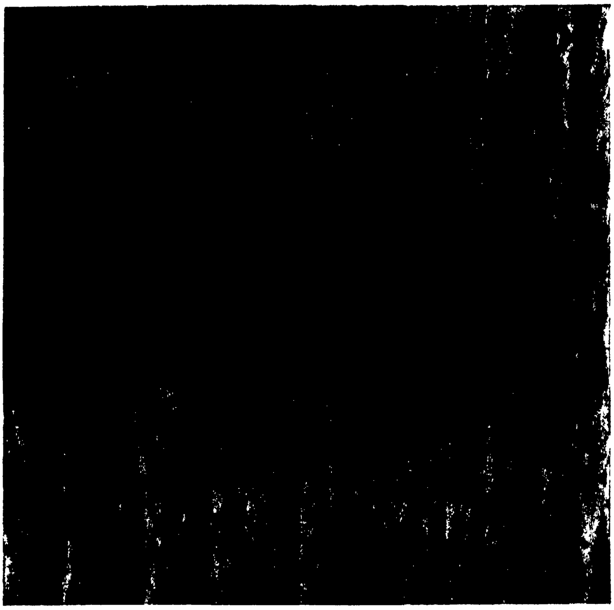

FIG. 758. Longitudinal section of a degenerating nerve, showing recent fragmentation of myelin. Osmic acid. × 200.

Repair or Regeneration of Nerve. Following upon **degeneration,** if the general continuity of the parts is preserved (experimentally, this can be attained by making use, not of a severing cut, but of a crushing injury which destroys the contained delicate nerve-fibres within the substance of the nerve, but leaves the continuity of the tougher and more resistant ensheathing tissues comparatively intact), and, if other circumstances are favourable, more particularly an adequate blood-supply and the absence of sepsis, there occur **a series of reparative processes**—complete or incomplete, as the case may be. With regard to the mechanism by which regeneration is brought about, there has, until comparatively recently, been some uncertainty, varying views being held as to whether the repair starts from the distal end of the central or upper portion, or from the proximal end of the peripheral part. For convenience, we shall speak of the former as the " central " and the latter as the " peripheral " end or portion of the divided or injured nerve. It is agreed by practically all observers that, in both the severed ends of the nerve, the cells of the sheath of Schwann—from whatever source these may themselves be originally derived embryologically—proliferate and become closely arranged in long tubular strands ; and all recent investigation, experimental in animals and clinical in man, goes to prove that these cells, both in the central stump and in the peripheral part of the divided nerve, undergo proliferation from **both** of the severed ends and attempt to bridge the gap if it is not too extensive. This proliferation is, however, often distinctly more active from the **peripheral** or distal end, and may take place at first fanwise, until some of the proliferating and projecting elongated cells, feeling their way, as it were, upwards towards, or perhaps in some chemotactic way attracted by, the proximal portion of the nerve, succeed in bridging the gap. Then, and only then, do the " parenchymatous " **nerve-fibres grow downwards from the central portion of the nerve** into the channels or sheaths thus prepared for them by the Schwann-cells and connective-tissue sheath, and the continuity of the nerve-fibres is thus restored **from above downwards.** The " centralists " are therefore correct in stating that the essential axons or nerve-fibres themselves grow down from the upper into the lower portion of the nerve ; but the " peripheralists " are also correct in so far as they aver that the scaffolding or bridge-work into which the axons penetrate from above can be and is grown largely from, and prepared by, the Schwann-cells, as well as other fibrous-tissue components of the sheath, **of the peripheral part** of the nerve. Some proliferation of the Schwann-cells of the proximal stump takes place, even when the guidance of the scaffolding from the lower part is missing or the gap is too great to be bridged ; but in that case the proliferation is apt to take the purposeless form of the production of an indefinite bulb-like growth—as in the so-called " stump- " or " amputation-neuroma," a misleading name, as explained on pp. 316 and 1141, the condition being in no way neoplastic.

Regeneration of nerve after section is brought about in much the same way as that following degeneration ; but, if the gap is too wide to be bridged, the axons developing from the central portion of the nerve, and any proliferating sheath-cells accompanying them, no longer have the remnants of the original sheath to guide them, and, in their "search" for the peripheral part of the nerve, they may take a tortuous course. If a temporary " scaffolding " is supplied to fill the gap, for example, by placing in it a transplanted length of nerve [1]—preferably a living graft derived from another, or best from the same, individual (these have been called respectively " homografts " and " autografts " by surgeons)—regeneration is in some degree facilitated and the course taken by the regenerating fibres rendered more direct. In the **surgical repair** of severed nerves, the best results (where no sepsis has supervened), follow primary suture—or some of the recently-introduced methods of " plastic " approximation and union. Mitchiner [2] points out that, as is to be expected, the nearer to the body the nerves of limbs have been severed, the more prolonged will be the period before recovery in the longer peripheral portion is complete. He gives two-and-a-half to three years as the probable interval required for recovery when the sciatic nerve has been divided and sutured in the upper part of the thigh, and a year or eighteen months or longer in the case of an analogous wound in the upper limb. If repair has not been previously effected, surgical interference after a period of two years is unlikely to be of much avail.

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[1] " Treatment of Gunshot Wounds of Peripheral Nerves," by Hugh Cairns and J. Z. Young, Oxford, *Lancet,* 1940, *ii,* 123 ; " Fibrin Suture of Peripheral Nerves," by J. Z. Young and P. B. Medawar, *ibid.*, 126 ; and " Nerve Regeneration," by J. Z. Young, W. Holmes and F. K. Sanders, *ibid.*, 128.

[2] " War Wounds and Air Raid Casualties," *Brit. Med. Jour.*, 1940, *i,* 124.

NEURITIS. In previous sections of this chapter we have had occasion to emphasise the frequently **multiple nature of the causation**[1] of many "diseases" and "symptom-complexes" which have their main, or sometimes only their subsidiary, seat in the nervous system. This holds good particularly for affections of the **peripheral nerves;** and many pathological states of these, previously regarded as infective or inflammatory and labelled more or less indiscriminately as "neuritis," are now attributed more correctly to various **nutritional deficiencies** and **metabolic abnormalities**—these either acting alone as the direct cause, or combining with toxi-infective and other factors to bring about the condition indirectly. When the lesions produced in nerves are not directly and technically "*neuritic*," *i.e.*, inflammatory in origin, the term "neuropathy" has been suggested to replace it, but this word itself is rather too vague in its significance to be really useful in this particular connection. The word "neuritis" is now so firmly established, not merely in popular parlance, but in medical literature itself, that, with this preliminary explanation and apology for our own rather indefinite employment of it, we feel ourselves compelled, for lack of a better and more convenient term, still to use it (in this connection *see also* footnote on p. 1077).

We have already referred to the degenerative nerve-lesions or so-called "neuritis" of beri-beri (pp. 444–5 and 1077) associated with **vitamin-deficiency** (especially of B_1) and to similar or analogous degenerative lesions of nerves, and of nerve-tracts and cells within the neuraxis, as well as in other disorders such as Addisonian anæmia, diabetes and other forms of glycosuria, pregnancy, and analogous conditions and disorders. It may also be noted here that such vitamin-B_1-deficiency tends, in **children,** to lead to the production of **muscular dystrophies** (p. 1243), but, in **adults,** to an **involvement of the neurone,** *i.e.*, the unit composed of cell-body, nerve-fibre and end-organ (*e.g.*, the motor nerve-endings or end-plates); whilst in syphilitic patients the combination of the syphilitic infection and avitaminosis leads to the development of tabes dorsalis (p. 1016); and, in alcoholic subjects who suffer from insufficient vitamin-intake or absorption, the result is "alcoholic polyneuritis," sometimes as part of the "Korsakow-syndrome" (p. 1051). It is pointed out, however, by Walshe[2] that, as had already been demonstrated in some of the early experiments on pigeons, deprivation of vitamin B_1 alone is *not* in itself sufficient to produce the characteristic picture of a true **multiple symmetrical peripheral neuritis.** For example in beri-beri, the accompanying phenomenon of **involvement of the myocardium,** and in a certain proportion of instances, **of the central nervous system** itself (with the development of symptoms of mental disorder), is also part of the usual syndrome. In the absence of carbohydrate from the diet, animals deprived also of vitamin B_1 do *not* develop neuritis and myocarditis, and Walshe therefore suggests that the clinical picture of a typical case of polyneuritis (which, as he emphasises, also includes myocardial involvement) is produced in whole or in part by a breakdown, at some point in its course, of the process of the carbohydrate-metabolism in the nerve-cells and heart-muscle. This breakdown takes place only under the *combined* influence of the absence of vitamin B_1 and the presence in the diet of a sufficient quantity of the necessary carbohydrate—in this instance in the form of the polished rice; and the failure occurs at the stage of the formation of pyruvic acid (pp. 444–5), which substance, however, is not itself regarded as the causal toxic agent. In support of this view, he points out that birds and human subject alike can be deprived of vitamin B_1 without the subsequent development of polyneuritis and myocarditis, if at the same time *no carbohydrates* are included in the diet. In normal circumstances, the vitamin B_1 acts as a catalyst in the carbohydrate-metabolism of the nerve-cells and the heart-muscle (p. 1077).

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[1] The word "*multiple*" here has, of course, no reference to the designation "multiple neuritis," where the term implies that *many* nerves are involved.

[2] "Ætiology of Polyneuritis," by F. M. R. Walshe, London. *Lancet*, 1941, *i*, 33.

The general condition, healthy or otherwise, of **nerve-fibres** is intimately bound up with that of the neurone-bodies or " nerve-cells " from which they are derived and of which they are integral component parts or processes; and therefore, where these cells are also themselves affected by such pathological states, the term **neuronitis,** to include an affection of its whole structure, is useful; whilst **radiculitis** and **radiculo-neuritis** are conveniently employed to denote lesions believed to begin, or have their main seat, respectively in the intradural spinal nerve-roots, or in these and the adjacent extradural spinal nerve-roots, or in the nerve-roots and the adjacent extradural portions of the spinal nerves. The word **polyneuritis,** replacing the older term " multiple neuritis," is used to imply that the lesions are widespread or perhaps even general throughout the peripheral nerves, and the terms **polyradiculitis** and **polyradiculo-neuritis** are similarly employed when the changes affect a large number of these roots or the roots and adjacent proximal parts of the spinal nerves. The study of lesions localised to the **nerve-endings,** motor, sensory or secretory, and also of abnormalities in their functions, especially in the part they play in the humoral transmission of nerve-impulses to their effector-organs, is a subject still calling for farther detailed investigation, for example in connection with diseases such as myasthenia gravis (p. 1245) and other varieties of neuro-myopathy and muscular dystrophy (pp. 1169–70 *et seq.*, and 1243–4). For full information on these subjects, reference should be made to special textbooks and papers.[1]

The clinical results of " neuritis " are varied and manifold according to the type of nerve affected and the extent and severity of the lesion. **Motor neuritis** will lead to paresis or paralysis of muscles, with flaccidity and wasting: **sensory neuritis** to neuralgias, paræsthesias, anæsthesia and trophic disturbances: implication of nerves to **glandular** structures may lead to abnormalities of secretion. A **mononeuritis** will be limited, a **polyneuritis** more extensive, in its results. Where particular portions, distal or central, of nerves are especially liable to be affected, the sequence of the symptoms may suggest, say, an " ascending neuritis," a " radiculitis " or a " neuronitis."

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[1] For example, the late Dr. Kinnier Wilson's " Neurology " (pp. 970 and 975 *et seq.*), which may also be consulted by those who wish for detailed clinical descriptions of the effects of lesions of the intradural spinal nerve-roots, extradural spinal nerves, nerve-plexuses, and individual peripheral nerves, as well as for clinical accounts of the many varieties of polyneuritis (" peripheral " or " multiple neuritis ").

See also Croonian Lectures on " The Clinical Aspects of the Transmission of the Effects of Nervous Impulses by Acetylcholine," by Francis R. Fraser, London, *Brit. Med. Jour.*, 1938, *i*, 1249 *et seq.*: and Linacre Lecture on " Biological Thought and Chemical Thought," by Sir F. Gowland Hopkins, Cambridge, *Lancet*, 1938, *i*, 1147 *et seq.*, including " Humoral Transmission of Nerve Impulses," p. 1201: " What we know to-day is briefly this: The impulses carried by nearly all the efferent neurones of the peripheral nervous system liberate in the tissues the substance acetylcholine; the exceptions being those carried by the post-ganglionic fibres of the true sympathetic system; but these liberate, alternatively, adrenaline. It is the special chemical nature of these two relatively simple substances that determines the effects observed on stimulation of peripheral nerves and constitutes a link between events in the nerve and events in the tissues."

Although the causes of neuritis are almost innumerable, a few of them may for convenience be grouped as follows :—

1. **Neuritis of traumatic origin.** The damage to the nerves may be due to practically any variety of trauma : for example, bruising and contusion, or cuts, tears, gunshot or other wounds, by which complete or partial division of the nerve may be caused. In other instances, the nerves become implicated in dislocations, fractures and callus-formation, or in scar-tissue. Pressure of a crutch (" crutch-paralysis ") on branches of the brachial plexus in the axilla, or compression of the musculo-spiral nerve between the humerus and the edge of a chair or table (as in " drunkard's paralysis "), or of a tight bandage, splints or plaster, on a limb, each may cause damage to nerves, for example, those of the affected limb may be the seat of neuritis in Volkmann's contracture and paralysis (p. 1251), with the production of severe pain, hypersensitiveness or anæsthesia and trophic changes in the skin of the hand or, less frequently, in the foot.[1] Similarly, **occupational** types of neuritis may be produced by the use of particular tools, whilst exposure to poisonous substances will bring some of these into the next group.

2. **Neuritis of Toxi-Infective Origin.** This group includes most of the cases of **polyneuritis** or **multiple peripheral neuritis** associated with or following **infective diseases** such as diphtheria, typhoid or scarlet fevers, measles and whooping-cough, and acute and other forms of rheumatism, as well as more localised varieties, as in the virus-produced forms such as herpes simplex and herpes zoster. A further group consists of those caused by **toxic substances** such as alcohol, carbon monoxide, carbon bisulphide and benzene, phosphorus, and the metallic poisons—lead, arsenic, mercury, zinc or copper ; and so-called " autotoxic " forms occurring in metabolic diseases such as diabetes and different varieties of renal disease. In some instances, the lesions in the nerves are due probably to the action of products of bacterial or other forms of infection or of disordered metabolism, and sometimes to a combination of both—these in many instances, as previously noted, acting in patients already suffering from **vitamin-deficiency,** more especially of vitamin B_1. The neuritis, sometimes severe, but usually more or less transient, which occasionally follows the **therapeutic administration of serum,** and which supervenes perhaps a week to a fortnight after the injection of anti-diphtheritic or anti-tetanic or other variety of serum, is probably a foreign-protein-susceptibility phenomenon, and its commonest site is the region of the neck, shoulder and upper limbs. In the epidemics in America of what is known as "**jake-paralysis**," a severe form of polyneuritis was produced by the substitution of the poisonous **triorthocresyl phosphate,** for the fluid extract of ginger (" jake ") in the manufacture of a popular variety of " soft drink."

Acute Febrile, Toxic or **Infective Polyneuritis** or **Polyneuromyelitis.**[2] This form of "polyneuritis" sometimes occurs in epidemics, as in the "Épidémie de Paris" of 1828, described at the time by Graves as "a paralysis creeping from the extremities towards the centre." As implied by the names in the heading of this paragraph, the cases of this group are characterised clinically by an acute febrile onset, and the occurrence of motor, and usually, though perhaps in lesser degree, sensory, neuritic signs and symptoms, with, as a rule, recovery in a few days or weeks. The cerebrospinal fluid generally shows an increase of coagulable protein, often only slight, but sometimes considerable, and with little or no accompanying increase of cells. The disease has to be distinguished from acute poliomyelitis and epidemic encephalitis (pp. 105 and 109), and also from various forms of neurosyphilis (p. 1002), and some of the myopathies (p. 1243). A neurotropic virus has been suspected as the cause, but its presence has not yet been established. In some analogous diseases, the actual carriage of an infective agent, *e.g.*, the virus of poliomyelitis (pp. 105–6) is known to take place by way of the interior of the nerves themselves.

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[1] Section on " Ischæmic Myositis," in " Clinical Study and Treatment of Sick Children," by John Thomson, Edinburgh, 3rd Edition, 1921, p. 707.

[2] *See* Kinnier Wilson's " Neurology," 1940, p. 298, where he writes : " Pathologically, the cord, root ganglia, and peripheral nerves are diffusely affected by toxi-degenerative change. . . .

A severe form of polyneuritis, with paresis or paralysis of both arms, both legs, or all four extremities, is described as attacking **children after certain acute infectious diseases** such as influenza, measles or whooping cough, the distal portions of the limbs being usually first and most severely affected.[1] It is possible that some of these are analogous to, or even examples of, the post-infectious encephalitis and encephalo-myelitis described on p. 99.

In individual cases of "polyneuritis," *e.g.*, in the acute febrile type, certain of the **cranial,** as well as the **spinal, nerves** may be affected, for example the facial, or perhaps the oculomotor and the other nerves supplying the eye-muscles; or the tongue, pharynx and œsophagus may become paralysed. **Post-diphtheritic paralysis,** which may supervene in from a week to one or two months after the onset of sore throat (which may be comparatively slight and may perhaps not have been recognised as diphtheritic), usually attacks first the soft palate, supplied by the glosso-pharyngeal, and, later, perhaps the pharynx and œsophagus, the muscles of the eye (with the development of squint and paralysis of accommodation) and paresis of the muscles of respiration (including the diaphragm) and—most serious complication of all—of the myocardium. There is frequently paresis of the lower, less commonly of the upper, limbs, or the neck and back. Similarly, various sensory disturbances may be noted. For descriptions of "supra-orbital," "dental" and other forms of "trigeminal neuralgia," "sciatica," "brachial" and innumerable other localised varieties of "**neuralgia,**" in so far as these are, or are thought to be, distinguishable from "neuritis" of the various nerves involved, we refer our readers to textbooks of Clinical Neurology and to the writings of Wilfred Harris [2] on the subject.

Evidently, then, 'polyneuritis' is a misnomer, or at least scarcely represents the facts, clinical and pathological; the condition should preferably be regarded as a polyneuromyelitis, or, as I once suggested, a polyneuronitis. But the latter term is objectionable . . . the inference is that its seat is spinal rather than, or as much as, peripheral."

[1] "The Clinical Study and Treatment of Sick Children," by John Thomson, Edinburgh, 3rd Edition, 1921, p. 604.

[2] "Neuritis and Neuralgia," 1926: and "The Facial Neuralgias," 1937: both Oxford Medical Publications, by Wilfred Harris, who, in reference to "Paroxysmal Trigeminal Neuralgia (Trigeminal-Tic)," in *Brain*, 1940, **63**, 215, writes: "I wish to reiterate here my previously expressed opinion (1926) that peripheral sepsis, such as dental caries, pyorrhœa, antral abscess and sinusitis are the prime causes of the disease": and, on p. 213, he makes the observation that patients with disseminated sclerosis are particularly liable to trigeminal tic—commonest in

In these groups and varieties of "neuritis," an attempt is sometimes made to differentiate between "parenchymatous" and "interstitial" forms, but it may be taken as axiomatic that, if one of these elements of the nervous structure is affected, the other will also be involved; though doubtless, as in analogous conditions of other tissues and organs, the more delicate structures—here the nerve-fibres, axons and myelin-sheaths—will suffer greater damage in greater degree than the hardier and more resistant connective tissue of the nerve-sheath. The latter may be stimulated to chronic proliferative fibrosis by an infective disease such as syphilis; or again, similar proliferative changes in the sheath may be the sequel of toxic and degenerative lesions of the nerve-fibres; and in many instances the two series of processes—toxic, degenerative and regenerative in the parenchymatous nerve-fibres on the one hand—and on the other the acute, sub-acute and chronic inflammatory and proliferative changes in the connective tissues of the sheath—continue side by side, though the relative intensity of each may vary at different periods in the course of the disease as a whole.

In these toxic forms, the nerve-trunks become swollen and of a reddish or pinkish-white colour, with extensive degenerative changes, producing widespread paralysis, as is seen sometimes in cases of **diphtheria.** In these forms, and probably in that due to **lead-poisoning,** changes occur also both in the nerve-endings in the muscle and in the muscle itself. In the nerves, all degrees of degeneration, from simple swelling and beading of the axons and myelin of the medullary sheaths, to complete destruction of the whole structure, may occur (Figs. 758 and 760, pp. 1178 and 1188). Usually, there is proliferation of the neurolemma-nuclei. In cases due to diphtheria, the nerve-sheaths, blood-vessels, and lymph-spaces, are sometimes the seat of an inflammatory reaction in addition to the degeneration of the nerve-fibres, the two processes, as explained in the preceding paragraph, taking place side by side.

In **alcoholic polyneuritis,** the process is generally subacute, and, as noted elsewhere (pp. 445 and 1180), the toxic action of the alcohol is practically always associated with B_1-hypovitaminosis. The changes vary considerably, and, in some patients, paralysis occurs without much evidence of degeneration. The axons are affected early, and the changes in them are accompanied by proliferation of the connective-tissue cells of the endoneurium, perineurium and epineurium. The blood-vessels or vasa nervorum are dilated, and leucocyte-infiltration is sometimes a prominent feature. The nerves of the legs are, in most cases, the first to be affected.

In **Raynaud's syndrome,** the lesions are found especially in the corresponding regional sympathetic ganglia, *e.g.*, in the stellate ganglia when the upper limb is affected (pp. 167, 187, 244, 483 and 1190: and Figs. 764 to 768, pp. 1193 to 1197), and in the nerve-fibres derived from the ganglia and passing to the arteries in the periarterial plexuses.

In **beri-beri** or **endemic polyneuritis** (*see also* pp. 445 and 1180), the nerves of the lower limbs especially are liable to become involved, but the vagus, and its roots and nuclei in the floor of the fourth ventricle, the phrenic, and the vaso-

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women and not infrequently bilateral—because: "Any individual whose peripheral nerve-endings in the sinuses or dental nerves have been exposed to sepsis, and who may therefore be said to be vulnerable to T.T. (trigeminal tic), will be therefore more likely to develop it if he, or rather she, has disseminated sclerosis."

motor nerves of the face, are not infrequently affected. Secondary lesions supervene in the muscles (pp. 261–2), the fibres of which are diminished in size, have a homogeneous appearance, and show proliferation of the sarcolemma-nuclei, with, in addition, a considerable increase in the supporting fibrous tissue. Involvement of the myocardium, as explained on p. 1180, is also characteristic of the beri-beri syndrome.

In the **toxi-degenerative forms of "neuritis"** due to **mineral poisons** (p. 262), all the structures of the neurones suffer, though in some instances the axons may persist for a considerable time, whilst degeneration of the medullary sheaths tends to take place early in the course of the disease—sometimes only over short lengths of the nerve, *e.g.*, involving one or more nodes of Ranvier. Along with these lesions in the peripheral nerves there are associated changes in the neurone-bodies or "nerve-cells" of the ventral horns; and, in certain cases (in poisoning with both lead and arsenic) thickening of the connective-tissue septa of the nerve-sheaths, and leucocyte-infiltration take place.[1]

In **lead-poisoning,** the **motor neurones** and their roots and fibres are affected more than the sensory, those of the forearms and hands especially being involved, producing the characteristic "wrist-drop"; and, similarly, **extensor** groups may be selectively attacked in the lower limb. The nerves of the larynx occasionally are affected. Oculo-motor paralysis occurs, and optic-nerve atrophy is not infrequent. The lesions of plumbism appear often to be more of the nature of a "poliomyelopathy" and "encephalopathy," or a "neuraxitis," *i.e.*, a combination of these generalised lesions, rather than a mere "peripheral neuritis." When the cells of the ventral horns are attacked, a form of "progressive muscular atrophy" (motor-neurone disease, p. 1169 *et seq.*) acute, subacute or chronic according to the severity of the lead-poisoning, ensues. In the acuter forms of lead-encephalopathy, meningitic symptoms, and endarteritis, with minute hæmorrhages and patches of softening in the brain, and a retinitis are found.

In the chronic forms of lead-poisoning, papillœdema and perhaps optic-nerve atrophy and blindness may occur, as well as involvement of other cranial nerves, producing, for example, ocular and other palsies. **In the cerebrospinal fluid,** a moderate pleocytosis of 50 or 100 up to perhaps 250 cells per c.mm., mainly small lymphocytes, an increase of total protein of 50 to 100 mgr., a slight excess of globulin, and sometimes of sugar (corresponding to a similar rise in the blood-sugar) are the usual but not invariable findings. The results of lead-poisoning in other organs and tissues are described elsewhere—the secondary changes (wasting and paralysis) in the muscles on p. 262: the "blue-line" on the gums on p. 233: and degenerative changes in the kidney in so-called "lead-gout" on p. 218. For its effects on the blood, including the production of the characteristic anæmia, see pp. 655 and 660.

Arsenical poisoning (cf. pp. 233 and 655) resembles lead-poisoning in its method of attack on the neuraxis and peripheral nerves, the **extensor groups** of muscles of the forearm and leg being frequently the first to suffer, apparently not so much on account of any excessive use of these muscles themselves (as was at one time thought likely in the case of house-painters) as owing to the localisation of the lesions in the corresponding motor neurones in the ventral horns of the cord and the consequent changes in the nerves arising from these. This "polyneuronitis" is part of a general neuraxitis like that previously described as occurring in lead-poisoning. In arsenical poisoning, the **optic nerves** are particularly liable to toxi-degenerative changes—the so-called "optic neuritis," for which special watch must always be kept in all cases under treatment with arsenical preparations. For detailed descriptions of the signs and symptoms due to these lesions produced by arsenic, as well as by mercury, manganese and other rarer metallic poisons, special works on medicine and toxicology should be consulted.

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[1] Kinnier Wilson (*loc. cit.*, p. 732) makes the apposite remark in this connection: "Toxi-degeneration cannot be confined to segments of the nervous system existing solely for purposes of description"

Carbon-monoxide poisoning, much commoner now than in the past because of the presence of this dangerous gas in the exhaust-fumes of the internal-combustion engine, as well as owing to its escape from improperly constructed and insufficiently ventilated gas-stoves, produces, not only important changes in the blood (p. 596), but serious toxi-degenerative lesions in the nervous system, acute and chronic, local or widespread, and affecting nerve-cells (cortical, central and spinal), glia and blood-vessels—the basal ganglia, the globus pallidus especially, being liable to selective attack (p. 1072).

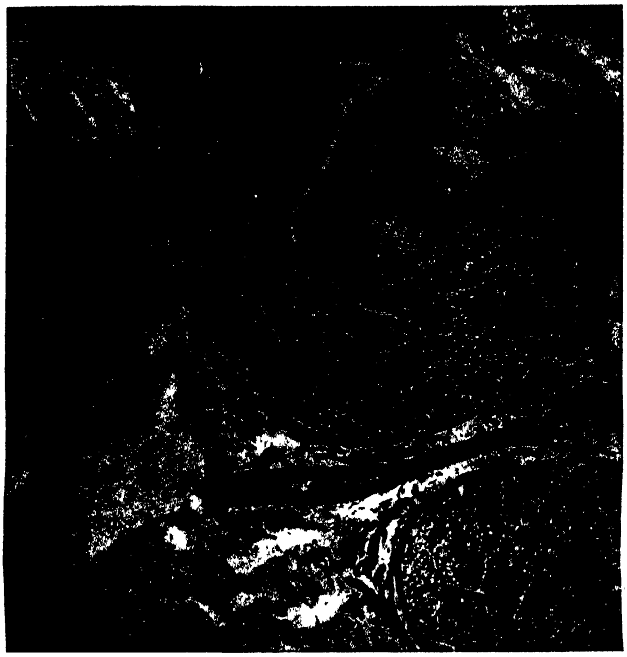

FIG. 759. *Myxœdema: transverse section of a nerve,* showing mucinoid ("myxomatous") areas in the supporting connective-tissue, and also some patches of degeneration in the nerve-bundles themselves. (van Gieson's method.) × 60.

The "neuritis" of **diabetes** and of various forms of **nephritis,** is a purely toxi-degenerative lesion, with no evidence of any accompanying inflammatory element in its causation. Changes of the nature of arteriosclerosis are generally found in the small blood-vessels, and may, in part at all events, be responsible for the changes in the nerves. Degenerations are found in the dorsal columns of the cord, and in the motor cells of the ventral horns. In the nerves, the degenerative process attacks especially the medullary sheaths, with fragmentation and absorption of the myelin. Only a few fibres in a bundle may be affected. The axons become beaded or varicose, but their continuity may to a considerable extent be preserved. In some cases of **myxœdema,** degenerative changes, usually mucinoid or "myxomatous"[1] in type, are found in nerve-sheaths (Fig. 759).

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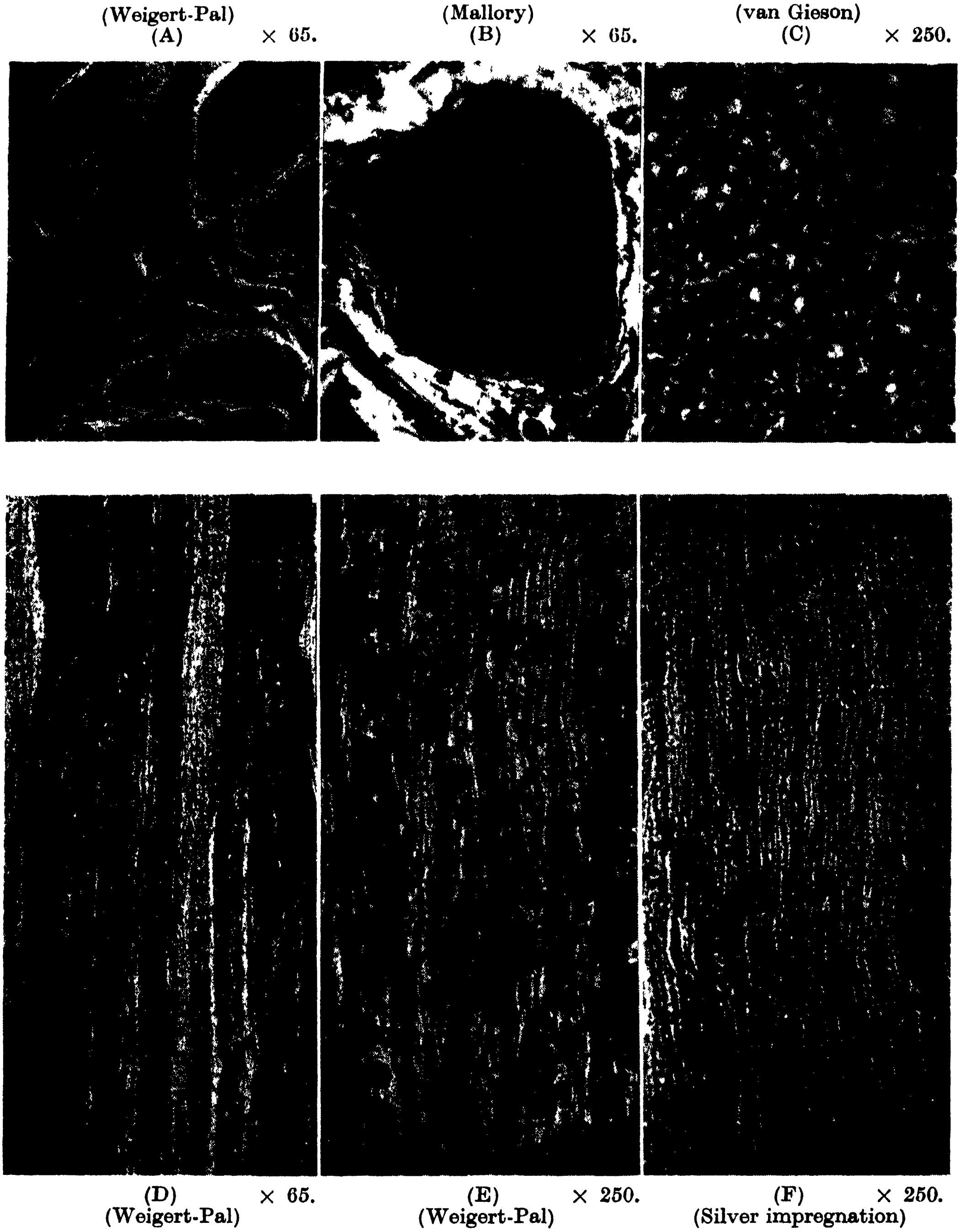
[1] With regard to the derivation and meaning of the word "myxomatous," *see* footnote on p. 301.

Neuritis due to the Local Action of Micro-Organisms. In the **maculo-anæsthetic** or "**nervous**" form of **leprosy** (p. 79), the nerves themselves become invaded directly by the bacilli, which tend to spread upwards or centripetally along them, either in continuity by infiltration or discontinuously by metastatic carriage by the blood in the vessels supplying the nerves, giving rise respectively to diffuse infiltrative or to nodular thickening, in both of which the bacilli are found in enormous numbers. The ulnar, median, peroneal and other nerves may thus become invaded, leading to the production of paralysis and wasting in the muscles they supply, and to sensory and trophic phenomena, for example, loss of pigment, and the production of white patches in the skin, and areas of anæsthesia (these not necessarily coinciding with each other)—and thus producing the lesions on account of which this form of the infection is termed "**maculo-anæsthetic,**"—as well as paræsthesias and perforating ulcers like those of tabes dorsalis. Of the cranial nerves, those most frequently attacked by leprosy are the facial and the trigeminal.

Hyperplastic Interstitial Neuropathy (or so-called "**Progressive Hypertrophic Neuritis**" or "**Chronic Hypertrophic Interstitial Neuritis**" of Dejerine-Sottas). We suggest that the first of these is the most appropriate name for this rare disorder, which is *not* "hypertrophic" (a term which, as we indicate on p. 264, would imply some useful purpose in the overgrowth); nor is it a "neuritis," *i.e.*, it is *not* inflammatory in nature. Its causation is unknown; but, though sometimes sporadic, it is often distinctly heredo-familial in its incidence. From our own study of the processes at work, we incline to the view that it may be a disorder of the same class as the von Recklinghausen's neurofibromatosis group (p. 1135), between the lesions of which and the abnormal growth and development of certain organs and tissues and even neoplasia, induced by the methods of experimental embryology (p. 291), there is also, perhaps, more than a chance resemblance.

Although problems of great pathological interest are involved, we need give only a brief description of the condition. Its onset is insidious, and usually noticeable first in infancy or early childhood; but it has also been described as occurring occasionally in adolescence or early adult life, though in these last instances it may have been previously present but unnoticed. There is progressive fibrous thickening of the various elements of the nerve-sheaths, usually diffuse, and rendering the swollen superficial nerves, for example the ulnar or the peroneal, not only palpable but even visible under the skin. The thickening affects also the spinal roots and root-ganglia and the cranial and sympathetic nerve-trunks. Apart from the chronic progressive fibrosis in the sheath, and degenerative changes in the axons and myelin-sheaths, the most characteristic phenomenon in the histology is the presence of concentric laminated "onion-like" bodies formed by proliferation of the sheaths of the nerve-fibres just external to the myelin-sheath, with increase in the number of the cells of Schwann, which show groups of perhaps half-a-dozen instead of the usual



(Weigert-Pal) (A) × 65. (Mallory) (B) × 65. (van Gieson) (C) × 250.

(D) × 65. (Weigert-Pal) (E) × 250. (Weigert-Pal) (F) × 250. (Silver impregnation)

FIG. 760. *Hyperplastic interstitial neuropathy* (or so-called "*chronic hypertrophic neuritis*") of the right ulnar nerve of a man aged sixty-five. The nerve was tough and "beefy" in consistence, rather than firm or hard. The various sections, transverse and longitudinal, all show the *chronic fibrosis* of the connective-tissue sheaths, most exaggerated in the perineurium, as shown in (B), but also diffuse in the endoneurium between the individual fibres (B) and (C). In the sections stained for myelin, (A), (D) and (E), the beading and fragmentation, and in many fibres the disappearance, of the *myelin-sheaths* are shown. In (F), the degenerative changes in the *axons*—irregular swelling and thinning, with the presence of curious little "kinks" and projections, and the disappearance of the axons from many of the fibrils—is demonstrated by the Gros silver-impregnation method. (Worster-Drought and Carnegie Dickson's case, W.E.H.)

single nuclei. In the centre of these "onion-bulbs"[1] there may still survive the central axis-cylinder with or without its enclosing myelin, or both of these may have degenerated and disappeared, though efforts at regeneration of the axons are occasionally seen. The changes in the muscles supplied by the degenerated nerves are those of paralysis and wasting; and the secondary deformities induced, especially in young children when affected, include claw-hand and club-foot, and sometimes various forms of spinal curvature such as kyphosis, scoliosis or a combination of both.

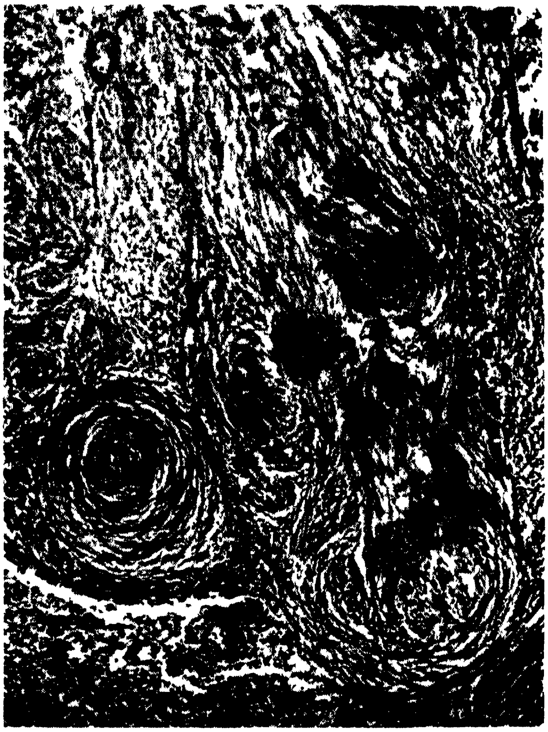


FIG. 761. *Neurofibroma* from a dorsal spinal root to illustrate the tendency of the ensheathing cells of the nervous system to form (*i*) *concentric whorls* and (*ii*) *parallel bundles and palisades*. (W.E.H. case.) Hæmatoxylin and eosin × 100.

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[1] With these compare the concentrically-arranged nodules seen in the nerves and nerve-roots, in the meninges, and in the various neurofibromatous tumours, in cases of neurofibromatosis (p. 1135 and Figs 726–8 on p. 1138: and Fig. 761 above), illustrating the tendency of the cells of the meninges and nerve-sheaths to form concentric structures resembling touch-bodies; and contrast this also with tendency to form parallel bundles and palisades corresponding to the formation of nerve-sheaths. (In this connection *see* footnote on p. 1139 *re* article by Worster-Drought *et al.*, *loc. cit.*, referring to these phenomena.)

SECTION XVI

MORBID CHANGES in the AUTONOMIC NERVOUS SYSTEM

The physiology, pathology and surgery of the Autonomic Nervous System are closely interrelated subjects upon which much new work has appeared in recent years.[1] Of its two great component parts, the **sympathetic** or **thoracic subdivision** deals especially with the **katabolic bodily processes,** largely through its influence upon the functions of the thyroid in relation to metabolism : upon the anterior pituitary in its *rôle* of master-gland presiding over the other endocrine organs, particularly in relation to bodily growth and the reproductive processes : and upon the suprarenals in relation to the government of the emotions through the mechanism of the circulatory system. The **parasympathetic** or **cranio-sacral subdivision,** on the other hand, is concerned mainly with the **anabolic** or **building-up** and **protective processes,** including any increase in the amount of the blood-supply required by the digestive tract, or the inhibition of any over-action of the heart. Many pathological states, both neurological and psychological, are concerned with, or appear to be the result of some "imbalance " between, the more or less opposed, or at all events opposite or complementary, functions of these two subdivisions of the autonomic system ; and, as an example of this imbalance or loss of co-ordination, we may cite the condition of " achalasia " of the various sphincter-areas of the gastro-intestinal tract to which allusion is made on pp. 713, 716–7 and 734.

We have elsewhere alluded incidentally to many of the problems connected with this system, *e.g.*, its relationship to the innervation of blood-vessels and their diseases (pp. 147 and 492) : involvement of the hypothalamus and its connections in various disorders and syndromes (pp. 807 *et seq.*, 819, 990 and 1121) : and also the consequences of certain lesions in sympathetic ganglia, for example in Raynaud's syndrome (pp. 167, 187, 244, 483, and 1184). Lesions such as various forms of neuritis which attack the nerve-trunks of the autonomic system and its nerves and their branches are in many ways analogous to those seen in the peripheral cerebrospinal nervous system, and we shall content ourselves here with a short note of a few of the outstanding pathological lesions which we have ourselves investigated, and which may be studied in certain of the **autonomic ganglia**—and in this connection it must be remembered that " the autonomic nervous system is a **functional,** and *not* an anatomical **division of the nervous system.**" The nature of the changes found in this system and their interpretation are in many ways analogous to those already studied in connection with the cerebrospinal system. Thus, inflammatory and degenerative lesions—in much the same way as they affect the corresponding structures of the neuraxis—produce changes in the ganglia and their nerve-cells, together with the axons and other constituent processes of these. The little groups of smaller perineuronal capsular cells which surround the ganglionic cells, undergo similar reactions, as does also the interstitial connective and fibrous tissue between the individual nerve-cells, around groups of these, and also that forming the main outer capsule of the ganglion continuous with the sheath of the nerve-trunk or branch on which it is situated. All of these component structures of the ganglion react in ways analogous to those already studied in Chapter II on Inflammation and Repair (pp. 15 to 54) : in Chapter III on The Granulomatous Diseases (pp. 55 to 95) : Chapter IV on Viral Infections (pp. 96 to 123) : and also throughout the rest of the present Chapter XXVIII on Diseases of the Nervous System itself.

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[1] *See*, for example, Samson Wright's " Applied Physiology," 7th Edition, Oxford University Press, 1940 ; and also " The Autonomic Nervous System," by Albert Kuntz, St. Louis University School of Medicine, U.S.A., 2nd Edition, Baillière, Tindall & Cox, London, 1934 ; and a résumé introducing a discussion in the Section of Neurology at the Centenary Meeting of the B.M.A., London, 1932—" Disorders of the Sympathetic Nervous System and their Response to Medical and Surgical Treatment," by Edwin Bramwell, Edinburgh, *British Medical Journal*, 1932, *ii*, 823, also contains useful information on this subject. *See also* G. E. Gask and J. Paterson Ross's " Surgery of the Sympathetic Nervous System," 1937.

Inflammatory Lesions, acute, subacute and **chronic,** produce any or all of the characteristic changes described elsewhere throughout our textbook—modified by the special structural characters, anatomical and histological, of the ganglia themselves. **Suppurative inflammation** may occur, usually as part of some neighbouring local, or perhaps widespread, infective condition. "Small-celled infiltration" is found in **subacute** and **chronic inflammations**, including those produced by the granulomatous diseases and viral infections. Proliferation and fibrosis of the interstitial framework and outer capsule, resembling or identical with those seen in the nerve-sheath in the various forms and degrees of neuritis already described, may take place ; and, along with these, one may find **degeneration** of the ganglionic cells themselves, with swelling, abnormalities in the distribution and perhaps the ultimate disappearance of the cytoplasmic chromatic or chromidial Nissl-granules : vacuolation of the cell-body, a

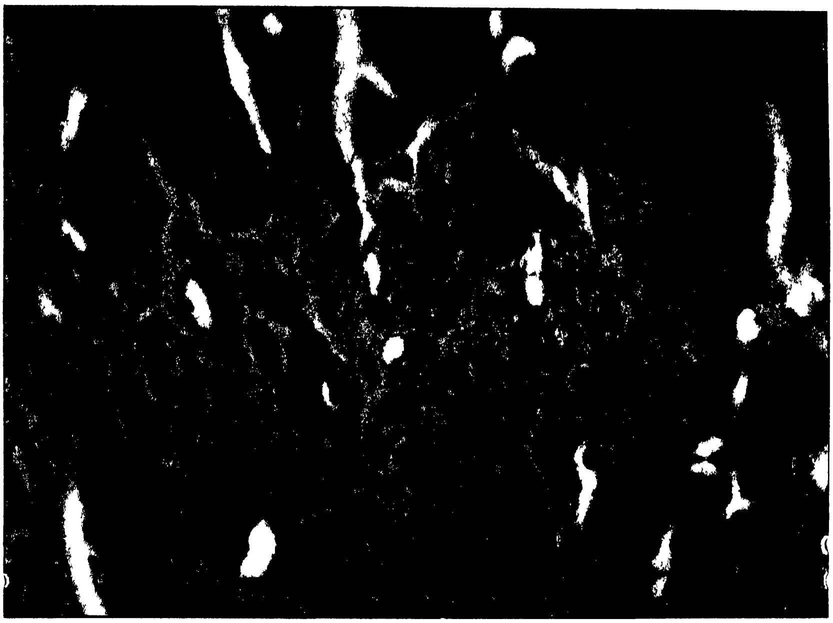

FIG. 762. *Transverse section of middle cervical ganglion involved in widespread chronic inflammatory thickening* of the prevertebral fascia and muscles, secondary to *chronic staphylococcal infection.*[1] The ganglion itself shows chronic inflammatory proliferation and fibrosis of the interstitial tissue, with degenerative changes in the nerve-cells (*see* text). Hæmatoxylin and eosin. × 400.

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[1] From a case of "Herniation of the Nucleus Pulposus producing Compression of the Spinal Cord (Complicated by 'Chronic Staphylococcal Granuloma')," Carnegie Dickson, *Proc. Roy. Soc. Med.*, London, 1936, 29 (Section of Neurology, pp. 61–69). *See also* Fig. 577, p 960 in the present Chapter : and pp. 1219–1223 in Chapter XXIX.

characteristic and not infrequent phenomenon (Fig. 766 (D) : increased or irregular and patchy pigmentation (Fig. 767 (F) and 768 (E)) : together with the usual nuclear alterations analogous to those described for the degenerative processes in nerve-cells in general—eccentricity, pyknosis, or more often chromatolysis—and perhaps breaking-up of the whole cell and its ultimate disappearance. One specially characteristic phenomenon is the proliferation and mobilisation of the perineuronal capsular cells, aided sometimes by other similarly mobilised phagocytic cells from other sources. These often invade and proceed to absorb the degenerating or degenerated nerve-cell and perhaps ultimately clear it completely away by the process of " neuronophagy," which has been previously described (pp. 1014 and 1118) as occurring to dying or dead nerve-cells elsewhere, a process analogous to the proliferation and phagocytic action of the neurolemma-cells of nerve-fibres.

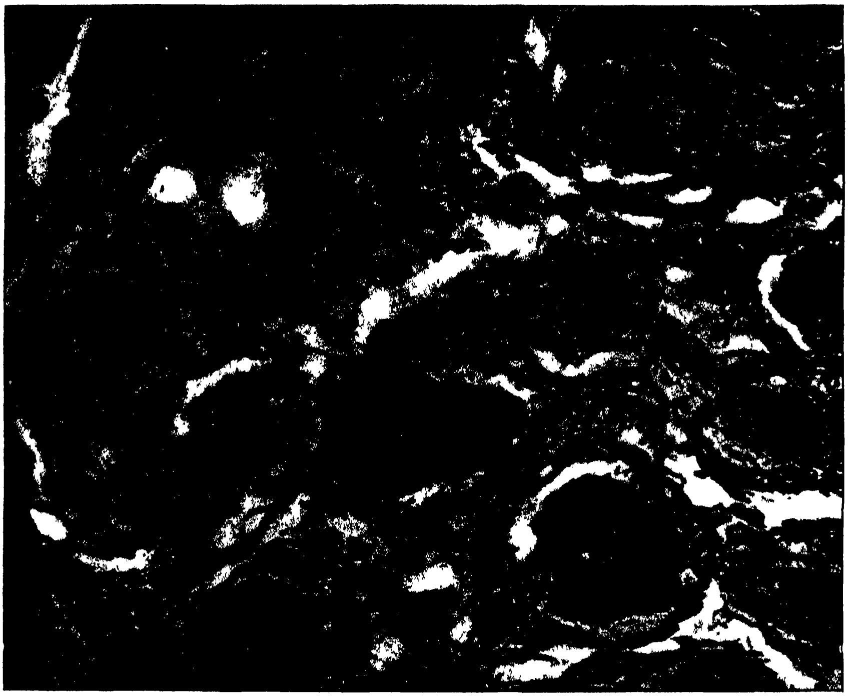

Fig. 763. *Section of fifth cervical dorsal spinal-root ganglion* from the same case (for comparison with the changes in the cervical sympathetic ganglion illustrated in Fig. 762). It shows mainly degenerative changes in the ganglion-cells. Mallory's connective-tissue stain. × 400.

We refer our readers to the annexed illustrations, in which many of these processes and phenomena can be seen, and which, therefore, need not be described in any great detail, as the reader can compare them with illustrations of normal ganglion-cells, etc., which he will find in his histological textbooks. In this connection, however, it may be well to note that, in the **normal histology** of the ganglia, there is a wide range of variation even in health, for example between the appearances of the ganglion-cells in the " resting " condition, and when they are examined after the occurrence of " fatigue." The size of the individual cells is extremely variable, and also their relative numbers, distribution and grouping, and the amount of intervening connective-tissue framework and the network of nerve-fibres and fibrils in the different ganglia—not only in different patients, but even in the corresponding ganglia on the two sides of the body in the same individual. A similar variability is to be found in the **pathological changes,** inflammatory and degenerative, which do not, as a rule, appear to be in any particular way "specific," but are similar to, or identical with, those already described in considerable detail in connection with other parts of the nervous system. Thus, in Figs. 765 to 768 from cases of **Raynaud's syndrome,** the changes are seen to be those of intercellular fibrosis, with corresponding diminution in the number and size of the ganglion-cells, etc., described in the legends of the illustrations.[2] (*See also* pp. 167, 187, 244, 483 and 1184.)

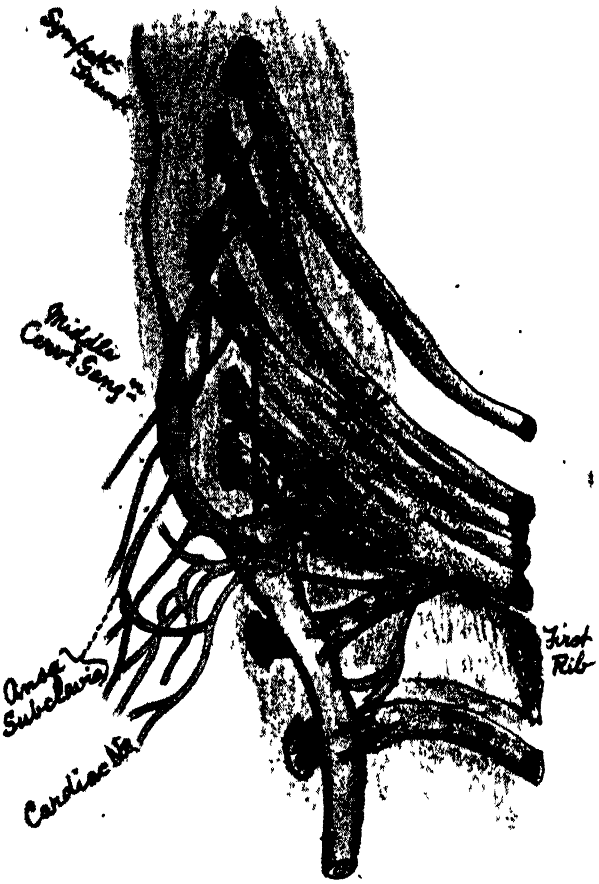

FIG. 764. *Diagram of the connections of the stellate ganglion* (composed of the fused inferior cervical and first dorsal sympathetic ganglia), removal of which for Raynaud's syndrome is described in the text. (*Cf.* Figs. 765 to 768.) (After Albert Kuntz, *loc. cit.*,[1] Fig. 4.)

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[1] *See* footnote, p. 1190.

[2] These sympathetic ganglionectomies for Raynaud's syndrome were performed at the West End Hospital for Nervous Diseases by Mr. Geoffrey Knight.

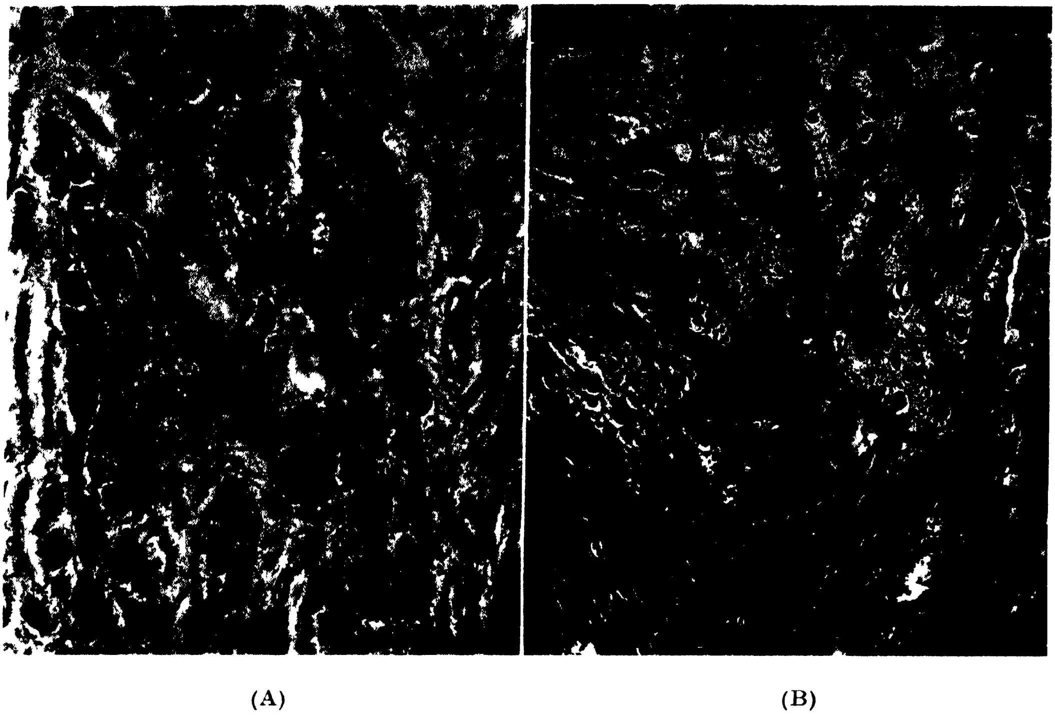


FIG. 765. *Raynaud's syndrome* sections of (A) the *left* and (B) the *right stellate* (*i e , the fused inferior cervical and first thoracic*) *sympathetic ganglia* (*see* Fig. 764), both showing fibrosis, with chronic degenerative changes in the ganglion-cells. (For details, *see* the following Figs. 766 to 768.) The section in (A) is from the junction of the connecting cord of the sympathetic with the upper pole of the ganglion The section in (B) is from a more central part of the right stellate ganglion. Mallory's connective-tissue method. × 75.

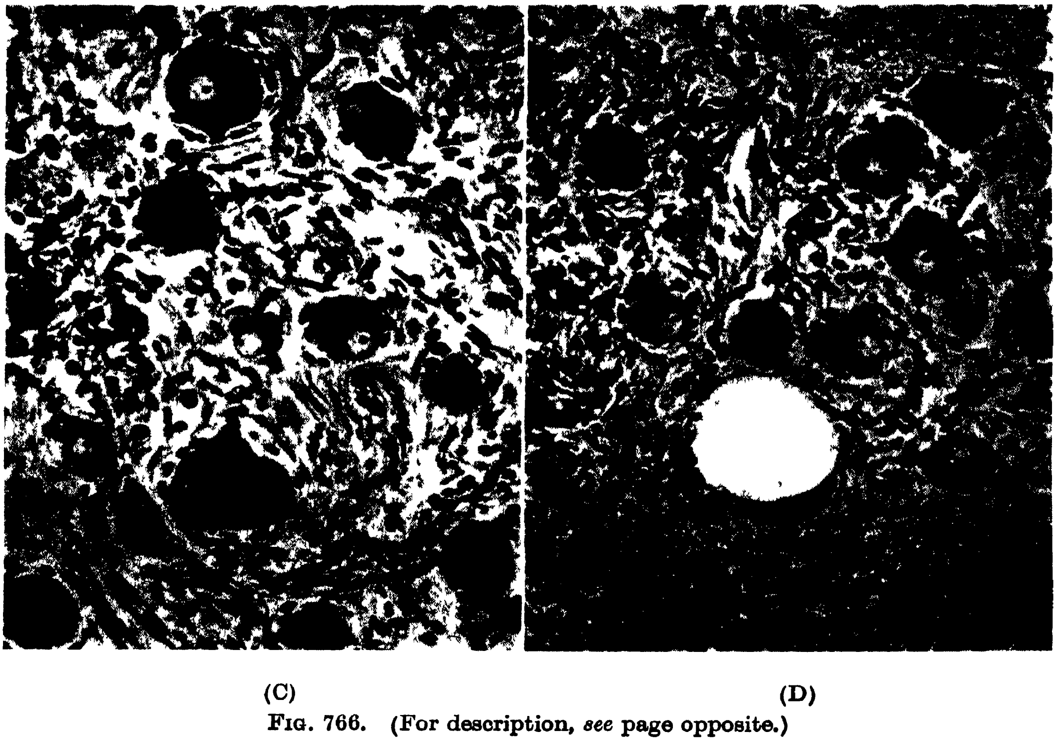
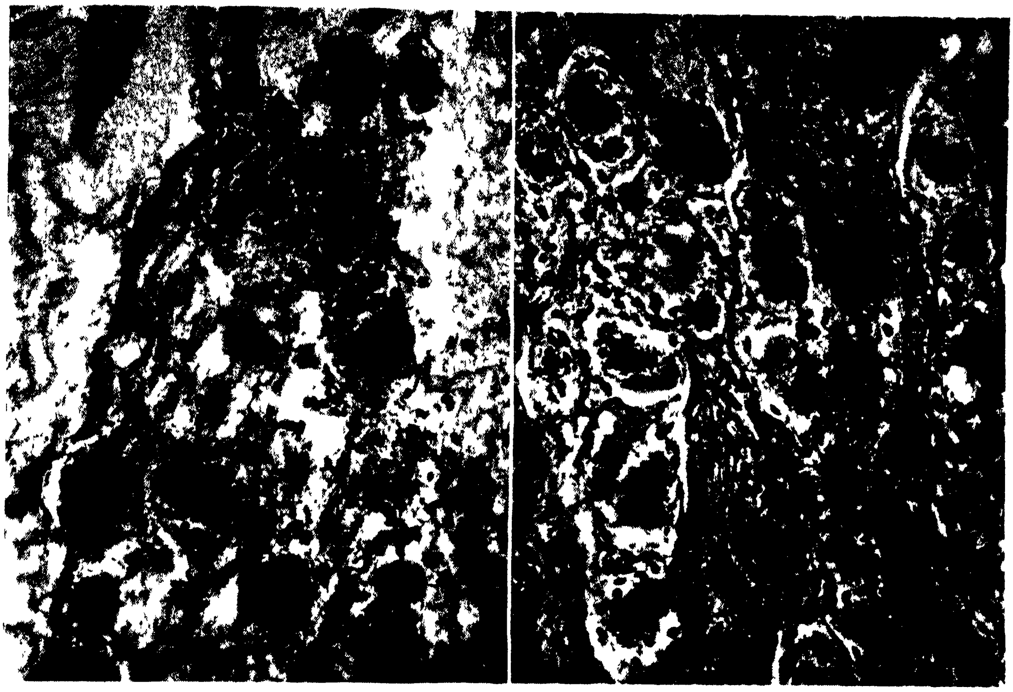


FIG. 766. (For description, *see* page opposite.)



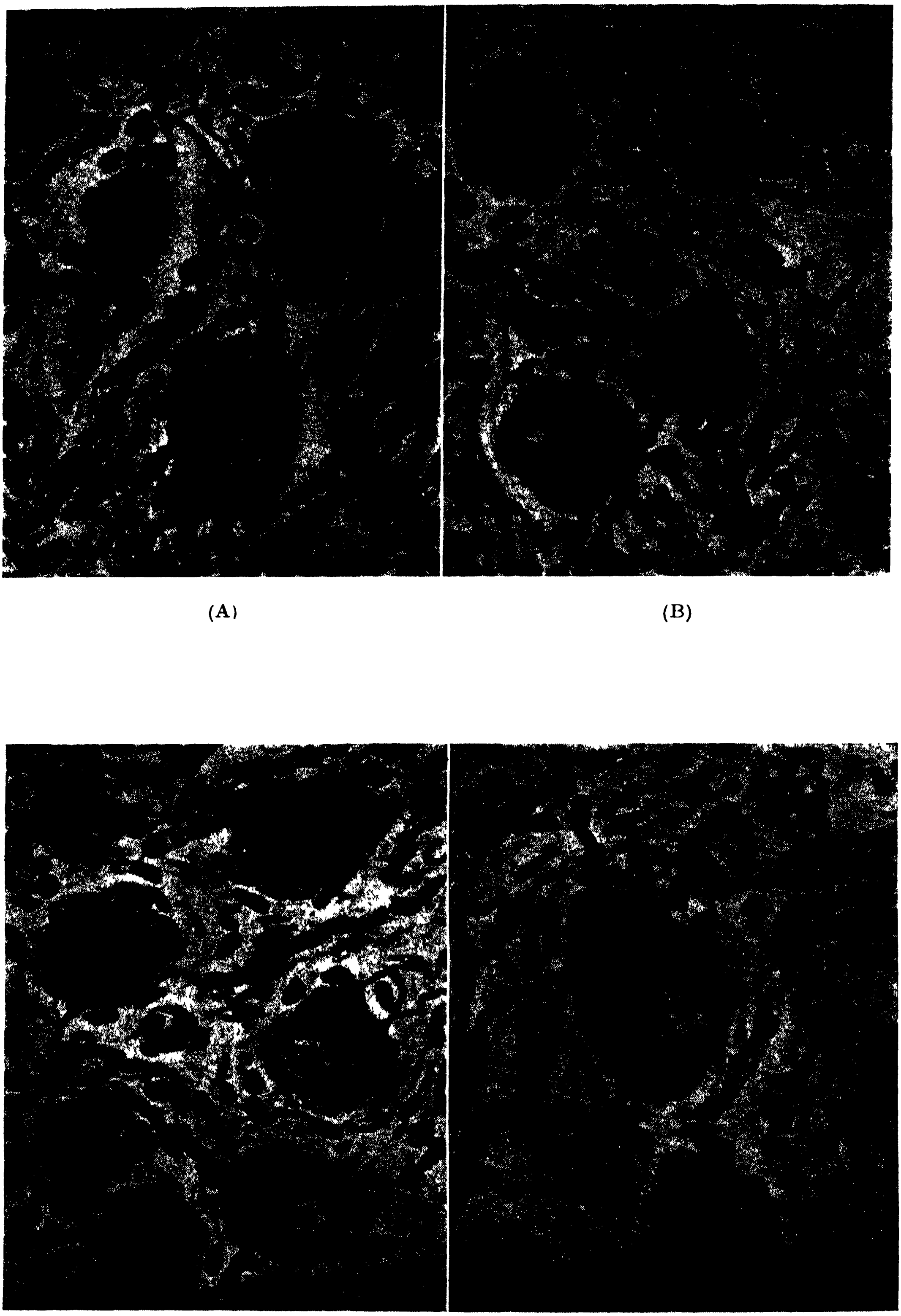
(E) (F)

FIG. 767. *Raynaud's syndrome :* similar high-power views of sections from the *right stellate ganglion* shown in Fig. 765 (B). In (E) "*neuronophagy*" of the ganglion-cells by the proliferating cells of their capsules is seen in this fibrosed area : whilst in (F) there is especially increased patchy pigmentation of the nerve-cells. Bielchowsky's silver-impregnation method. × 300.

FIG. 766. *Raynaud's syndrome* · high-power views showing details of the degenerative phenomena in the nerve-cells and the interstitial tissues of the *left stellate sympathetic ganglion,* a low-power view of which is given in (A) of Fig. 765.

(C) shows various stages of the degenerative process, including increased patchy pigmentation of some cells, in others both cytoplasm and nucleus are undergoing degeneration and disintegration. In (D) similar degenerative phenomena are illustrated, with, in addition, a very large vacuole in one of the cells (the contents of which in other (frozen) sections did not stain for fatty or lipoid material)—such vacuoles,[1] usually smaller in size than this example, being of comparatively common occurrence in degenerative conditions of sympathetic ganglion-cells. Both sections also show interstitial fibrotic changes. (Bielchowsky's silver-impregnation method. × 300.)

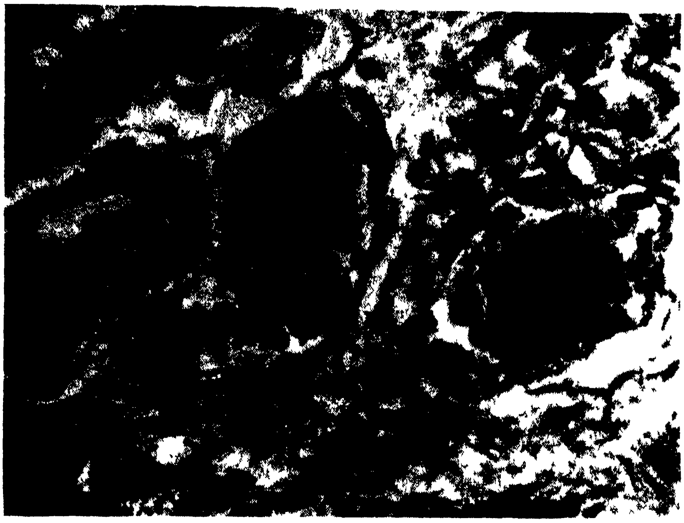
[1] **Vacuoles,** not unlike those which we ourselves have frequently found in the cytoplasm of the nerve-cells of the stellate and other **autonomic ganglia** in the human subject, are figured by Clark, Beattie, Riddoch and Dott, in Fig. 9, p. 13, of their book on "The Hypothalamus" (1938), as having been found by Gaupp and Scharrer in the nerve-cells of nuclei (*e.g.*, the supra-optic) of the **hypothalamus** in the squirrel and in man. The presence of colloid material in these vacuoles, they are inclined to believe, may be evidence of independent glandular **secretory activity** on the part of the nerve-cells of the hypothalamus as part of the autonomic system ; and it is interesting, to speculate upon a similar possibility in the case of autonomic ganglion-cells, though we have, so far, been unable to demonstrate the presence of any specific contents, either lipoid or colloid, in the paraffin, celloidin or frozen sections which we have examined. These authors also describe (and figure), in the case of the hypothalamus, as do we for the autonomic ganglia (Fig. 768 (A)), the not infrequent occurrence of *bi-nucleated nerve-cells.*



(A) (B)

(C) (D)

Fig. 768.



(E)

FIG. 768. *Series of frozen sections of the stellate ganglion* excised from a woman, aged fifty-nine years, suffering from *Raynaud's syndrome.* Oil-immersion photomicrographs illustrating *various stages in the degeneration and disintegration of the ganglion-cells* described in the text, with progressive breaking-up of the neurofibrillary network : proliferation and mobilisation of the cells of the perineuronal capsules, and invasion and neuronophagy by them of the ganglion-cells : eccentricity and chromatolysis of the nucleus of these nerve-cells : disappearance of the nucleolus and of the nucleus itself : and, finally, breaking-up and progressive disappearance of the entire cell.

In (A) one of the ganglion-cells has two nuclei— not an uncommon phenomenon in autonomic ganglia, especially in young subjects, but not so frequently seen in elderly patients such as this. In (B) some of the cytoplasmic processes or dendrites containing degenerating neurofibrils are seen. In (E) patches of pigment are shown in the disintegrating cytoplasm. Note also the irregularity and mobilisation of the cells of the perineuronal capsules and the degenerative changes in the intercellular tissue which contains the remains of neurofibrils amongst the swollen and proliferated connective-tissue framework of the ganglion. Bielchowsky's silver-impregnation method. × 850.

Changes in autonomic ganglia in multiple neurofibromatosis (pp. 1135–39) are illustrated on the next page. Fig. 769 shows an early nodule in a small ganglion from the neighbourhood of the left suprarenal : and in Fig. 770 much more advanced changes are illustrated from sections of the ganglion semilunare of the trigeminal cranial nerve.

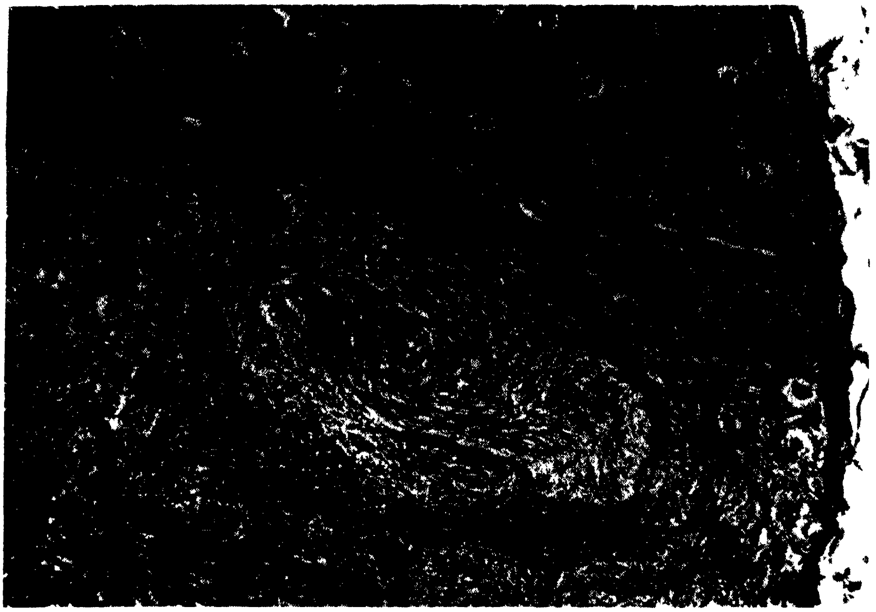


FIG. 769. *Multiple neurofibromatosis* in a man of twenty-five years : *section of a small sympathetic ganglion* from the neighbourhood of the left suprarenal. Low-power view showing the formation of *a small neurofibromatous nodule*, the structure of which may be compared with that of the tumours illustrated in Figs. 726–7 and 761, on pp. 1138 and 1189. Only a few surviving degenerated ganglion-cells are seen. Hæmatoxylin and eosin. × 100.

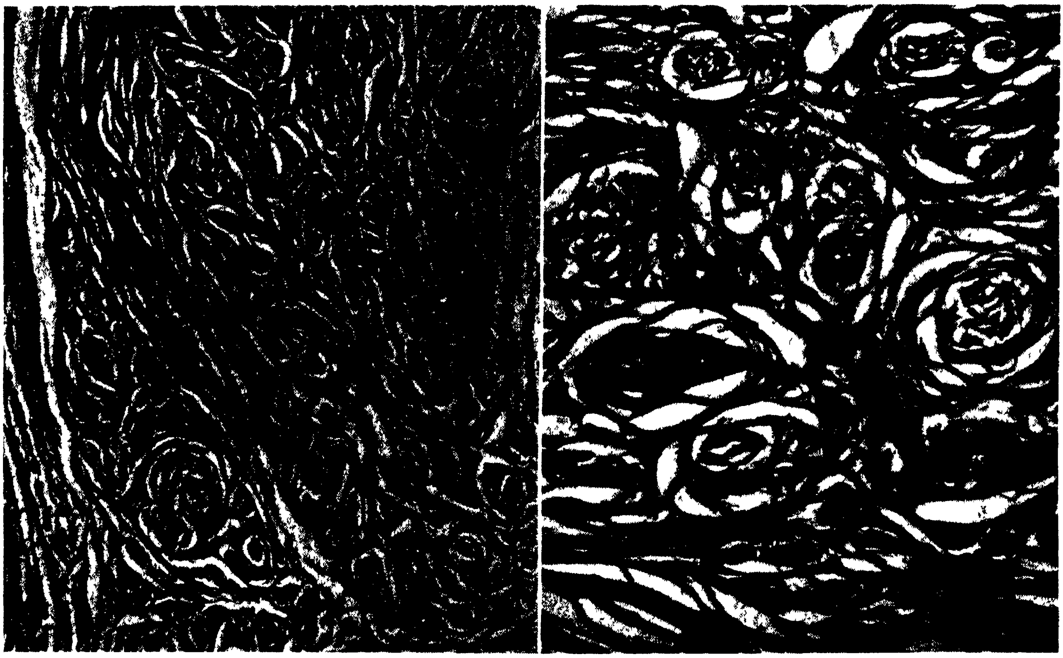


FIG. 770. *Trigeminal ganglion* (*ganglion semilunare* or *Gasserian ganglion*) on the sensory root of the fifth cranial nerve, from a case of *multiple neurofibromatosis* in a boy aged seventeen years (*see* footnote on p. 1139 and Figs. 721 and 723, pp. 1135 and 1136). Fibrotic changes, analogous to some of those occurring elsewhere in the nervous system in such cases, have taken place in the stroma of the ganglion, with the production of whorls of connective tissue around individual ganglion-cells which then undergo degeneration and disappear. Mallory's connective-tissue stain. × 75 and 300 respectively.

CHAPTER XXIX

DISEASES OF BONES : JOINTS : TENDONS AND MUSCLES

SECTION I

DISEASES OF BONE

BONE consists of a dense matrix arranged in layers—the lamellæ—impregnated with lime-salts, chiefly phosphate, and containing irregularly-shaped branching cells, the bone-corpuscles, enclosed in lacunæ, from which run branching canaliculi. The bony tissue may be either compact or spongy in character. In the spongy bone, the blood-vessels run in the interstices, supported by the marrow ; but, in compact bone, they are contained in the Haversian canals, round which the lamellæ are arranged in concentric fashion.

Immediately under the periosteum, the bone is denser than at other parts, the lamellæ here being pierced by canals for blood-vessels which join those in the Haversian canals. The periosteum is composed of two layers, the inner of which is highly vascular and contains numerous osteoblasts or bone-forming cells.

Bone is formed by the deposit of calcium salts and phosphorus (largely as a calcium phosphate), in an interstitial substance, the greater part of which is identical with the collagen-fibres of connective tissue. The relative amounts of the collagen-fibres and the salts fluctuate within certain limits. In old age, a deficiency in ostein—the organic residue of bone after the earthy salts have been dissolved out by acid—occurs, and in certain diseases the bones lose a large part of their salts. In **ossification in cartilage,** the cells become enlarged and arranged in definite rows ; and, in the matrix, as well as in and around the cartilage-cells, granules of calcareous matter are deposited. At the same time, the osteoblasts at the deeper part of the periosteum form fibrous lamellæ, in which they themselves become enclosed to form **bone-corpuscles.** Later, the lamellæ become calcified. This subperiosteal layer of bone extends inwards, the calcified cartilage being absorbed by it, and irregular spaces—the medullary spaces are formed, which become filled with **osteoblasts.** These osteoblasts, in their turn, produce new lamellæ, which become calcified. The absorption of the calcified matrix is effected by large multinucleated cells—the **osteoclasts.** The regular lamellæ are not laid down till some time after birth. The deposit of calcium and phosphorus in the ostein or osteoid tissue is a chemico-physical process ; but is determined to a certain extent by an enzyme (phosphatase) which is produced by the bone-cells, particularly in the deeper parts of the periosteum where the osteoblasts are specially numerous. This enzyme splits off the phosphorus from its organic combination and enables it to unite with calcium to form calcium phosphate in the bone-matrix.

At a later period, the cartilage, at one, or more usually at both, ends of the long bones, begins to ossify from a separate centre or centres. Normally, the **epiphyses** do not become joined to the shaft by ossification of the epiphyseal cartilages until the growth of the bone is completed. The bones increase in length in virtue of the growth of the cartilage which intervenes between the shaft and the epiphyses, and the gradual extension of the ossification into it. They grow in width by successive deposits of fresh bony layers under the periosteum, and, therefore, in surgical operations in which bone is removed, it is important, as far as possible, to avoid injury to the osteogenic layer of the periosteum and the epiphyseal cartilages. Some authors regard this osteogenic layer as belonging to the bone rather than to the periosteum, but, in the succeeding pages in our references to the formation of new bone, we shall assume that this layer is **periosteal.** In the growth of bone, the balance between the osteoblastic and osteoclastic processes is regulated by vitamin D and the secretion of the parathyroids (pp. 440–1 and 837–8). Calcification and ossification of cartilage

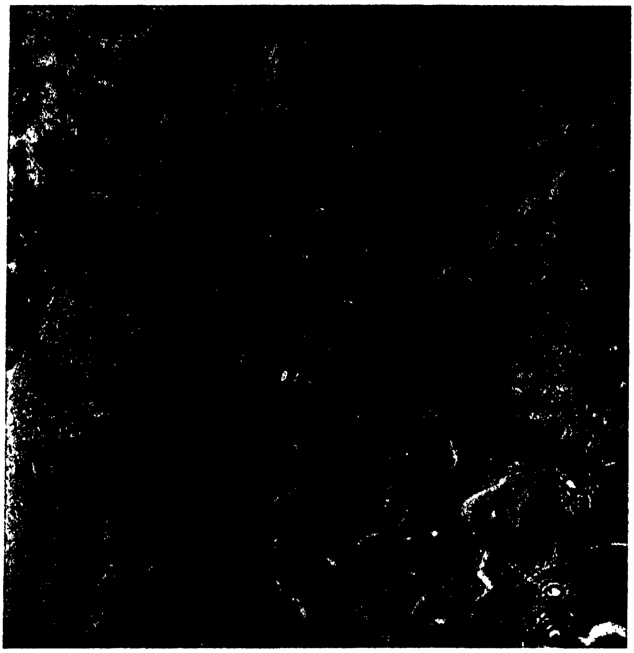


FIG. 771. *Transverse Section through Normal Compact Bone (Tibia)* : showing the Haversian canals, round which may also be seen the concentric lamellæ. Periosteum is shown at upper left corner. (By courtesy of the late Professor Alexis Thomson.) × 28.

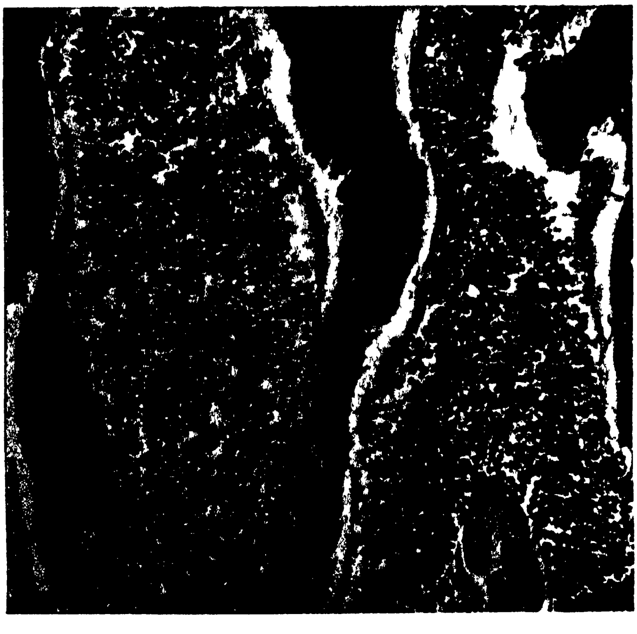


FIG. 772. *Longitudinal Section of the Upper End of the Tibia of an Infant* : showing spicules of newly-developed compact bone, with layer of osteoblasts on their surface : and cellular bone-marrow in the intervening spaces of the bone. The white spaces are due to artificial retraction. (By courtesy of the late Professor Alexis Thomson.) × 100.

may take place prematurely, and be the cause of a certain impairment of movement or, in the case of the skull, lead to the deficient enlargement of its cavity.

In **intra-membranous ossification,** the lime-salts are deposited in a fibrous tissue which contains numerous osteoblasts.

In studying the diseases of bone, it should be remembered that the formative activity of this tissue is retained more completely and efficiently than that of practically any other structure in the body : that the bones are constructed upon a definite plan which enables them to resist the strain of various mechanical forces of necessity applied to them : and that, therefore, plastic overgrowth, guided by a definite architectural design, may take place under the influence of various stimuli. Thus, where fracture or bending of bones has occurred, there may be overgrowth of osseous tissue for protective purposes ; but, in addition, there is a definite plan of reconstruction in order to meet the new lines along which pressure or stress may be applied to the injured bones.

MALFORMATIONS OF BONE. A premature coalescence or **synostosis,** of the bones, or of component parts of a bone, leads to various deformities. Among the commonest of these malformations are synostosis of the sacro-iliac articulation, which produces narrowing of the pelvis, either on one side, or on both sides, depending upon whether there is affection of one or both articulations. Synostosis of these joints and of the pubic symphysis in women may interfere with childbirth. Synostosis of the epiphyseal cartilages in growing bones leads to " shortening "—or, more accurately, deficient growth and elongation—and other abnormalities in the long bones. Premature synostosis of the sutures of the cranial bones was formerly thought to be the cause of microcephaly, this in turn being believed to prevent the growth and proper development of the enclosed brain ; whereas, although this may occasionally be the explanation, smallness of the skull, and consequently of the head as a whole, is now regarded as the **consequence,** and not as the cause, of the more essential and primary phenomenon of **micrencephaly** or smallness of the **brain** (p. 1067 *et seq.*). There may also be abnormal **osseous union** between the component bones of the tarsus or carpus, and, associated with this or independent of it, **absence** of certain of the bones. Such malformations may be symmetrical on the two sides.

Absence of bones such as the clavicle, the lower jaw, the patella, certain bones of the skull, etc., are congenital defects. Deficiency in the neural arches is seen in cases of **spina bifida** (p. 1066). Excessive and irregular growth of bone occurs in **gigantism** and in **acromegaly** (pp. 810 to 815).

Cervical rib, developed in relation to the seventh cervical vertebra, is of not infrequent occurrence. Occasionally it is associated with the sixth cervical vertebra. It occurs either as a small bony enlargement which does not extend beyond the transverse process of the vertebra ; or is more complete and extends laterally and forwards into the posterior triangle of the neck, ending in a cartilaginous tubercle or a fibrous band which attaches the rib to its costal cartilage. Occasionally, a complete extra rib is developed. Part of the brachial plexus and the subclavian artery and vein arch over it, and its presence may be associated with phenomena such as paræsthesia of the areas of skin to which the nerves—especially the eighth cervical and first thoracic—are distributed, paresis or perhaps paralysis of the muscles supplied by the affected nerves, coldness and cyanosis in the hand and fingers, and even ulceration and gangrene of the ring and little fingers. These trophic phenomena are generally regarded as at all events partly the consequence of a disturbance of sympathetic innervation (especially the contribution from the first dorsal nerve as it passes over the supplementary rib) rather than as entirely the result of mechanical pressure, although rapid relief of the symptoms usually follows operative removal of the cervical rib, or may, in some cases, follow mere section of the scalenus anticus tendon, a procedure which relieves any undue pressure on the lower trunk of the plexus. The subclavian artery may be abnormally dilated and thrombosis in it is said to occur in some cases.

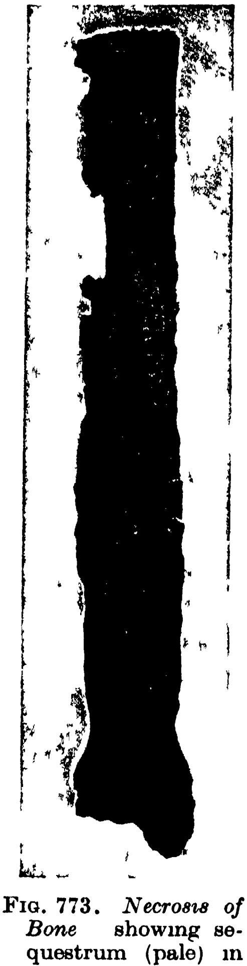


FIG. 773. *Necrosis of Bone* showing sequestrum (pale) in centre, surrounded by the "new case."

CIRCULATORY DISTURBANCES in BONE. Venous congestion and hæmorrhage may occur. The hæmorrhage which takes place either under the periosteum or into the bone-marrow may result from trauma, or be a manifestation of osteomalacia, scorbutus, purpura or hæmophilia. The effused blood may cause separation of periosteum from bone, and so bring about necrosis. Extensive hæmorrhage into the bone-marrow is sometimes observed in acute infective conditions, *e.g.*, streptococcal septicæmia.

INFLAMMATION — OSTEITIS, PERIOSTITIS, OSTEOMYELITIS :—

Most cases of inflammation in bone occur in childhood, when the tissue is still actively growing. The inflammation is often suppurative in character and due to pyogenic organisms, either introduced directly at the time of an injury, or carried by the blood-stream from distant infective foci in the skin, tonsils, or elsewhere, and lodged in the bone, possibly, in many cases, at a previously weakened focus. Inflammation of bone may be secondary to bullet- or other wounds, to septic infection spreading from the site of amputations, or to a compound fracture of any bone. In all these cases, the organisms are introduced from without and the inflammation is usually **suppurative** in character.

Abscesses form at, and in the neighbourhood of, the seat of injury, and may invade the medullary cavity, destroying the bone-marrow. **Thrombosis** of the veins is a frequent sequel, and, owing to disintegration of the septic thrombus, **pyæmic abscesses** may be produced, especially in the lungs and the walls of the heart. The injury may be slight, but the fact that the inflammation occurs frequently in bones which are exposed to external violence, and particularly in boys, points to injury as having an important relationship to the disease. The long bones, especially the tibiæ, are those most frequently affected; but the vertebræ, ribs and bones of the pelvis may

also become infected. Though various bacteria may be the cause of such acute suppurative conditions in bone, *Staphylococcus aureus* is the organism most commonly found, the term **staphylococcal fever** being sometimes applied to such cases. Any cause of general or local lowering of resistance, such as exposure to cold, malnutrition, or one of the exanthemata, is a predisposing factor.

The characters of the lesions vary considerably, depending upon the virulence of the organism and its invasive power, the seat of infection, and the resisting capacity of the patient. In weakly children, the lesion is commonly suppurative. In a long bone, the primary lesion is usually para-epiphyseal, *i.e.*, in the shaft on the diaphyseal side of the epiphyseal cartilage, but may commence in the epiphysis itself. The bone-marrow is affected early, and the inflammatory reaction spreads along the para-epiphyseal line and under the periosteum. In the early stage, there may be no obvious pus in the medulla of the bone—the marrow being merely red and congested; but, later, pus forms, fills the medullary cavity, spreads to the bone itself and invades the looser subperiosteal tissue. The spread to the neighbouring joint is arrested as a rule by the epiphyseal cartilage. Hæmorrhagic foci sometimes showing a white central point of pus—**pyæmic abscesses**—may be present in the lungs and myocardium even before the lesion in the bone-marrow has become purulent.

In some instances, the infection is mainly confined to the periosteum (**acute periostitis**), which shows all the phenomena of acute inflammation and suppuration, pus accumulating between it and the bone. In the majority of cases, however, the inflammation and suppuration tend to be more widespread, and to involve the periosteum (**periostitis**), bone (**osteitis**) and medulla (**osteomyelitis**); and pus may thus be present also in the substance of the bone and in the medullary cavity. **Necrosis of bone** is common and, in these cases, is caused partly by the local action of the bacteria and their products, but chiefly by the separation of the periosteum from the bone by the exudate, and the consequent cutting off of the principal blood-supply. The necrosis may be localised or may involve the whole shaft of a long bone, an epiphysis, or even some of the flat bones, *e.g.*, the skull. The dead piece of bone—or **sequestrum** —sometimes retains its form and general appearance, but it frequently becomes white, opaque, dry, and hard, and is surrounded by a mass of granulation-tissue, in which ossification may take place. Thus an irregular external "new case" or shell surrounding the dead bone may be produced (Figs. 773–4); and, in this, the sinuses through which the pus is discharged remain as permanent apertures. This new bone is, at first, soft and friable, but, later, becomes thick and dense, forming the **involucrum,** or case; and, eventually, it is strong enough to act as the shaft of the bone. A varying degree of absorption of the sequestrum may take place, and sequestra of small size are frequently discharged through a sinus. If the sequestrum is large, and has not, as is now the usual practice, been removed by operation, it may remain in position for years. One of the commonest sites at which sequestra are liable to be formed is the jaw, especially after dental extractions—small fragments of dead bone, *e.g.*, the alveolar margins, separating and being discharged before healing can take place.

Chronic Osteomyelitis. Localised abscesses may be found in bone, especially in the cancellous tissue towards the extremities of the long bones, usually in close proximity to the epiphyseal cartilage, *e.g.*, in the head of the tibia on the diaphyseal side of the cartilage (**Brodie's abscess** [1]). These abscesses, which usually become walled-in by a dense surrounding layer of bone, are more or less chronic, and in some instances may possibly have been tuberculous in nature; though, in others, **Staphylococcus aureus** has been isolated from them. Other examples of "chronic osteomyelitis"—by some writers regarded as "osteochondropathies" (p. 1241)—affecting special bones are usually known by the names of the authors who first described them, *e.g.*, **Köhler's disease** of the tarsal scaphoid, **Kienböck's sclerosing osteitis** of the carpal semilunar bone, **Osgood** and **Schlatter's disease** of the tubercle of the tibia, and **Legg-Calvé-Perthes disease** (p. 1241) of the head of the femur. In such cases, slow necrosis of the epiphysis of the bone, usually without the formation of pus, takes place. These lesions occur especially in young children. Trauma may be a predisposing cause of the various forms of chronic osteitis or osteomyelitis. Irritation may be kept up by the presence of foreign bodies or by portions of dead bone which act as such, or it may be the result of slowly-acting irritants, such as the organisms of tuberculosis or syphilis. Hæmorrhage and partial dislocation may occur and the condition of "slipped epiphysis" is probably a result of such a low-grade infection. These chronic infective agents or irritants stimulate the formation of granulation-tissue under the periosteum or in the medullary cavity. The granulation-tisssue cells may act as osteoblasts and produce new bone, with consequent thickening of the shaft; or, as osteoclasts, they may bring about rarefaction and absorption

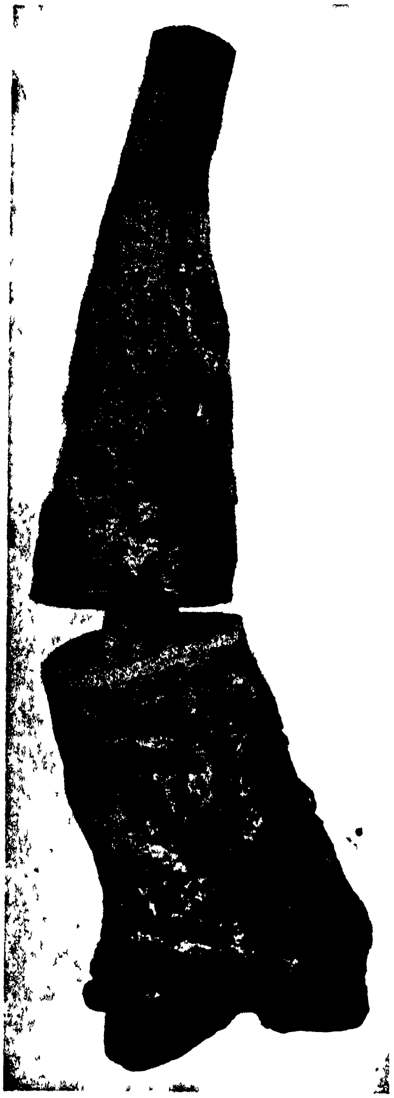


FIG. 774. *Necrosis of Bone*: around the sequestrum the "new case" has been formed. From a patient with chronic osteomyelitis of femur.

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[1] Sir Benjamin Brodie's first case (recorded in *The London Medical Gazette*, 1845, **36**, 1399) was in the *lower* end of the tibia in a young man aged 24, the specimen being still in St. George's Hospital Museum. The limb was amputated, and, from its examination, Brodie came to the conclusion that the leg might have been saved if the abscess had been evacuated by trephining the bone. The disease had been going on for some twelve years, and it has been suggested that, not only this particular case, but at all events some, of the examples of "chronic abscess" in the head of the tibia subsequently described by him—though usually regarded as cases of chronic staphylococcal infection—may, as noted above, quite possibly have been tuberculous.

(*cf.* Fig. 775). Commonly, the formative and rarefying processes are acting simultaneously and the bones become more cancellous and at the same time increased in thickness.

Typhoid osteitis is a well-recognised lesion occurring during or after an attack of typhoid fever, and is really a subacute or chronic osteomyelitis. It is seen most commonly in the tibia, the ribs and the sternum, but the vertebræ and other bones may be attacked.

"**Caries**" is a term applied to the softening and destruction of bone, and is seen especially in tuberculous affections, but may also result from osteomyelitis, and be associated frequently with necrosis. The bone becomes soft and spongy, and breaks down readily. Reference has been made to it under Tuberculosis of Bone (p. 66)

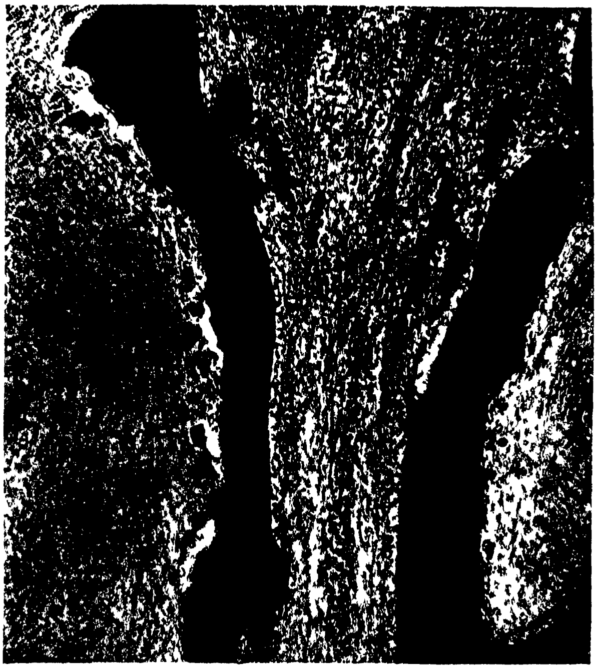

FIG. 775. *An Osteophyte,* in which the bone is undergoing absorption by osteoclasts lying adjacent to the bony trabeculæ. (By courtesy of the late Professor Alexis Thomson.) × 60.

Phosphorus-Necrosis (p. 708). This occurs among phosphorus-workers, and is supposed to be due to the local action of the vapour of yellow phosphorus. It begins in the periosteum—a great formation of new cancellous bone taking place on the surface of the upper jaw. Bacteria enter from the mouth, by way of carious teeth, and, after a time, the inflammation becomes suppurative, with the result that the periosteum is detached from the bone and necrosis, which may involve the whole upper jaw, takes place. The lower jaw may also be involved, and the sequestrum, which forms as a result of the necrosis, separates very slowly. It has been stated by several observers that this condition of "phossy-jaw," as it has been called, is due, in reality, to the presence of the tubercle bacillus—the poisonous action of the phosphorus preparing the way for, and perhaps also acting in conjunction with, that organism. The disease is now uncommon, on account of the substitution of amorphous phosphorus for the yellow variety in the manufacture of matches, and we have not personally had the opportunity of investigating the relationship of tuberculosis to the necrosis. Phosphorus-poisoning has now been recorded as due to absorption of phosphorus from certain types of German bullets (p. 197) when these have remained embedded in the tissues.

REPAIR OF FRACTURES :—

When a bone is fractured, there is generally some laceration of the periosteum and the surrounding tissues, with resulting **hæmorrhage.** There may be, and usually is, some **displacement.** Repair is brought about by the same series of reactions as occur in the healing of an incised wound in a connective tissue (p. 43), with, in addition, the special processes of bone-formation (p. 54); and the repair is sometimes delayed, or even prevented, by lack of apposition of the fragments, by movement, and by the presence of torn tissues such as muscle, or of excess of effused blood, between the broken ends of the bone, or by septic processes. In repair, the vessels in the bone, in the medullary cavity and in the periosteum, become dilated. There is transudation of lymph, with emigration of leucocytes and, if apposition of the fragments is maintained, these reactions last from one to six days.

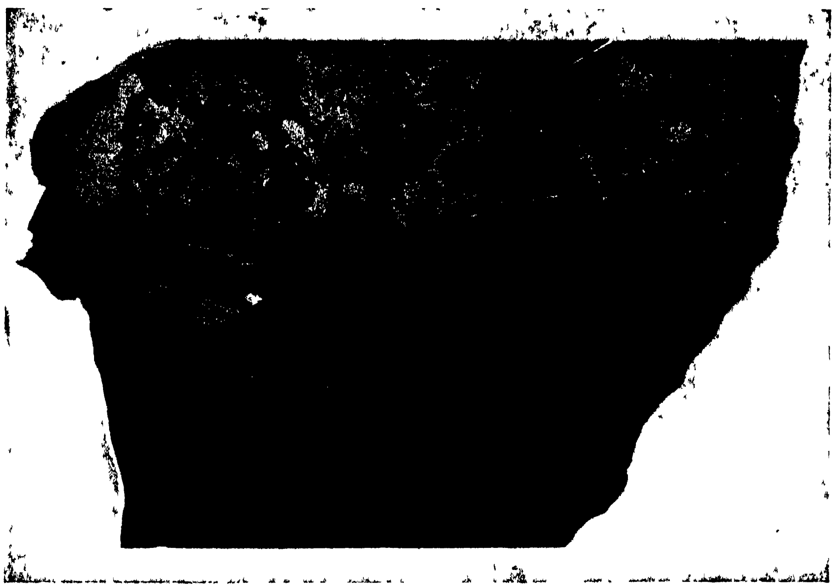

FIG. 776. *Horizontal Fracture of the Internal Malleolus* (three weeks): showing a zone of intermediate callus. (By courtesy of the late Professor Alexis Thomson.) × 4.

On the second or third day after the injury, the periosteum shows active cellular proliferation, especially in its deeper part; and there is also proliferation of the endothelial cells of the blood-vessels. These changes extend for some distance beyond the seat of fracture, and also invade the periosteum, separating its different layers. Similar reactions are seen in the bony tissue itself, and in the marrow. Young blood-vessels, arising from pre-existing vessels, pass into this cellular tissue, and any effused blood undergoes absorption. Thus, masses of vascular granulation-tissue, more or less extensive, are formed.

This **granulation-tissue**—many of the cells of which are multinucleated and correspond to osteoclasts in structure and function, whilst others are of the nature of osteoblasts—may become fibrous or cartilaginous ; but, usually, in the human subject, ossification takes place in its deeper layers, the new bone being formed in trabeculæ continuous with the outer layers of the original bone. Contemporaneously with this new formation of bone, absorption and modelling go on. The changes, in fact, are exactly analogous to those seen in normal development and ossification of bone. By the successive deposit of new layers, a large mass of **ensheathing callus**[1] may be produced. In the interior of the bone, and between the fractured ends if there is displacement, similar masses of callus are produced. The **internal callus** may almost completely fill the medullary canal ; whilst the **intermediate callus**—especially if apposition has been maintained—is usually small in amount, and is derived probably in part from the tissues in the Haversian canals, and in part by an extension from both the **external or ensheathing and internal callus.**

The **provisional callus,** thus formed, undergoes absorption by osteoclasts, new layers of bone possessing Haversian systems are laid down, and these are arranged so that they are adapted to the exact line of strain—the internal architecture of the bone often becoming greatly modified, especially if the union has taken place with the ends of the bones out of position. Sometimes, and especially if the parts have not been kept sufficiently at rest, ossification is imperfect, the ends of the fractured bones becoming united by tissue which remains largely fibrous in character, and a species of false-joint is thus sometimes formed, furnished, perhaps, with a cavity and with smooth articulating surfaces covered with fibrous tissue.

DISORDERS OF GROWTH :—

(*a*) **Reparative Overgrowth** is described under the formative type of chronic osteitis (pp. 1204–5), and in connection with the repair of fractures (pp. 1206–7).

(*b*) **Hyperplastic Overgrowth.** It is difficult or even impossible to differentiate some forms of hyperplastic overgrowth from those which are produced during the processes of repair. As a result of chronic irritation, there may be a true hyperplasia ; but the mode of production of the new bone is essentially the same as that which occurs in the process of repair. Thus, in the local formation of new bone in the region of chronic ulcers, or round a piece of necrosed bone, the new-formation is indistinguishable from the bone produced in the process of the filling-up of the cavity from which the necrosed portion has been removed. A more generalised hyperplasia is seen in syphilis and in poisoning with mercury. In the latter condition, the thickening of the bone is liable to occur especially in growing bones, and may be due to an interference with the normal absorption and modelling, rather than to an actual stimulative overgrowth.

Overgrowth, essentially different in its causation from that occurring in repair, may take place in certain situations, and may be confined to certain bones. Thus, with hyperactivity of the pituitary gland, and according to the age of the patient, the conditions of **Gigantism** and **Acromegaly** are produced (pp. 810 to 815). In the latter, enlargement and thickening of the bones, particularly of the fingers and toes, the lower jaw, the **maxillary part** of the upper jaw, and the malar, nasal, and frontal bones are present; and, not unusually, there is thickening of the bones of the pelvis, together with alterations of a similar nature in the sternum, clavicles, ribs, vertebræ, and other bones.

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[1] "Callus," *see* footnote on p. 54.

Local overgrowth of bone occurs at the sites of attachment of muscles on which there is special strain. These overgrowths constitute **osteophytes**—the best example being furnished by the so-called "rider's bone" at the lower attachment of the adductor magnus.

(*c*) **Neoplastic Overgrowth.** Definite bony tumours are described on p. 1225 *et seq.*

DISORDERS OF CALCIUM-METABOLISM AND CALCIFICATION :—

1. **"Osteitis" Deformans**[1] **(Paget's Disease of Bone).** This is a disease developing insidiously and usually only in the later age-periods. In it there is enlargement, with general thickening, of some of the bones, especially the tibiæ, clavicles,

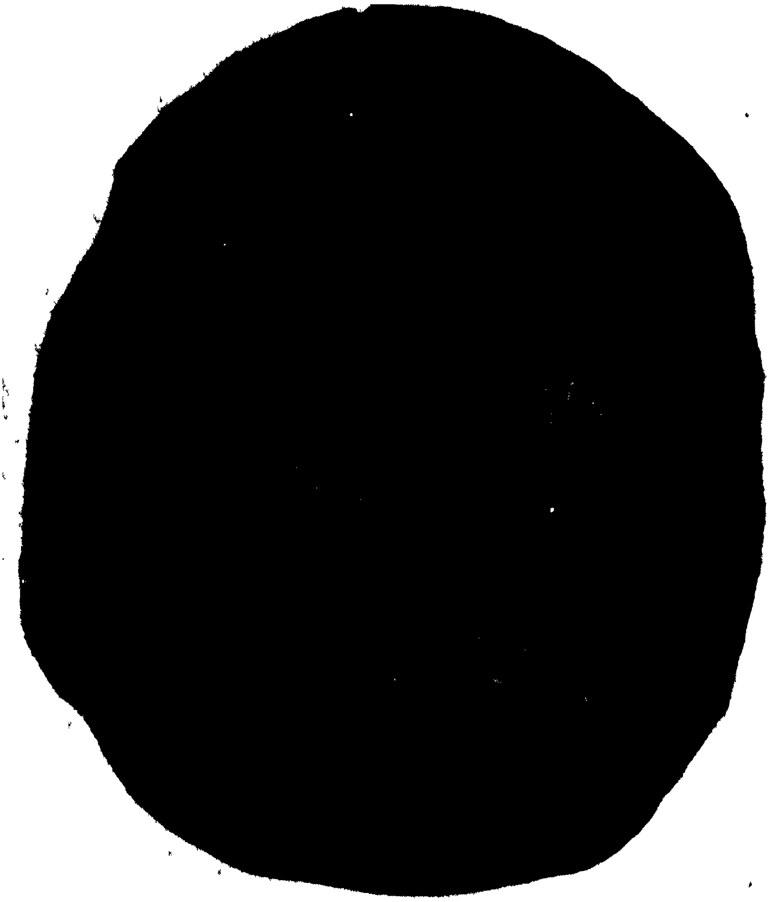

FIG. 777. *Paget's Disease of Bone (Osteitis Deformans)* : showing great thickening of bones of cranium.

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[1] The term "Osteitis" has long been applied to this and other *non-inflammatory* disorders of bone, and is therefore used here without necessarily implying its usual specific significance of an infective inflammatory condition.

and cranium. The bones are spongy, and, though greatly increased in thickness, are lighter in weight and softer than normal, but the consistence varies in different parts of the same bone. At places it may be possible to cut it with a knife, but

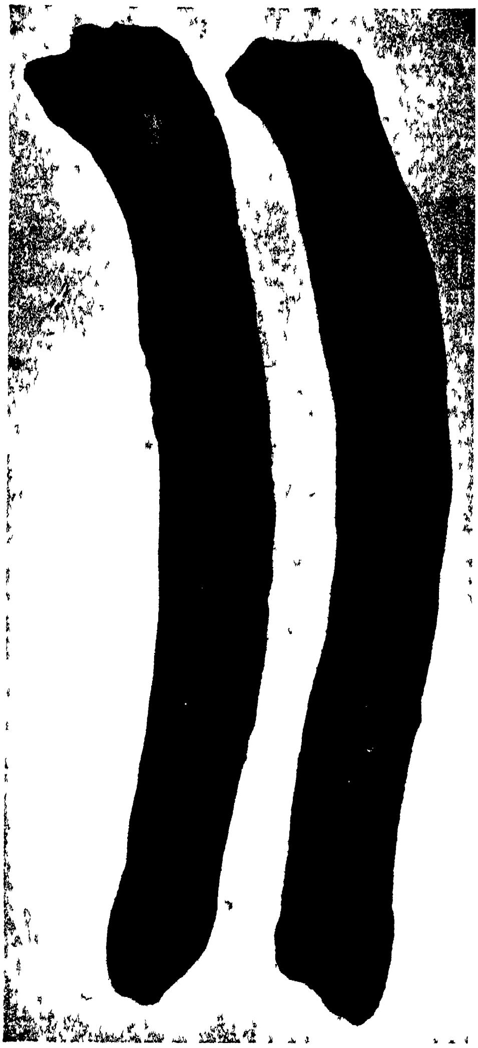
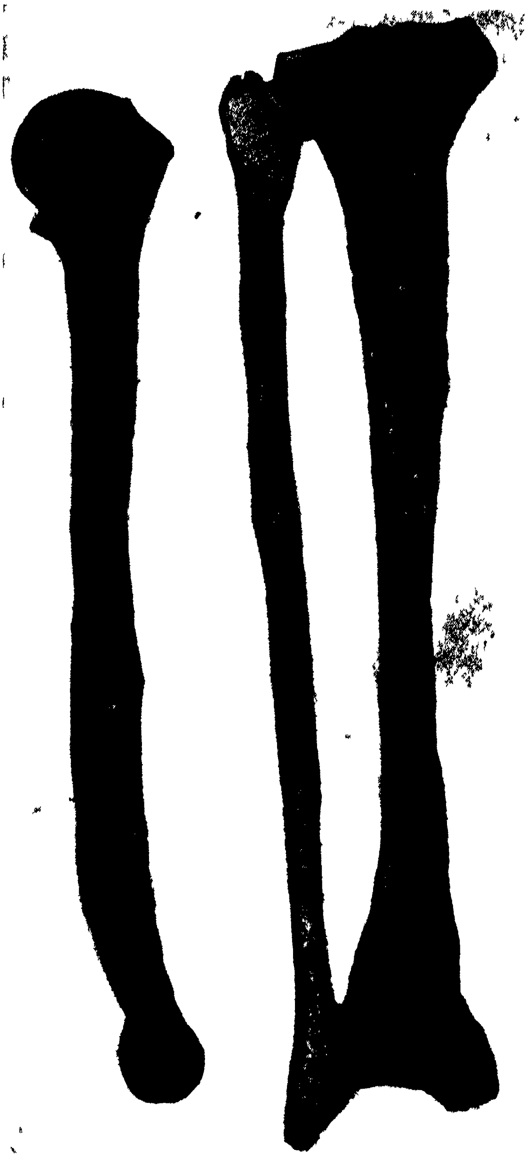


FIG. 778. *Paget's Disease of Bone* (*Osteitis Deformans*) The tibiæ are curved throughout their whole length, with the convexity of the curve directed forwards. The circumference of the shaft is uniformly increased from end to end.



(A) (B)

FIG 779. *Paget's Disease of Bone* (*Osteitis Deformans*) (A) humerus in section, (B) tibia and fibula showing irregular thickening

in other areas a thick deposit of hard subperiosteal bone is formed. The surface of the bone presents a finely pitted appearance. In the long bones, the medullary cavity is narrowed; and, in the lower limbs, the bones are usually bowed forwards and outwards. During the earlier stages of the disease, the changes are often more advanced in one bone than in others, and, usually, the bone of the hands and feet do not show any characteristic pathological changes. In the skull, there is very great thickening, with obliteration of the diploë, but the bone is more porous than normal. The head shows enormous asymmetrical enlargement, the temporal fossæ become shallow, and the forehead prominent and overhanging. There is no narrowing of the various foramina in the bones of the skull, and the facial bones are usually unaffected. The thoracic and lower cervical spine may show a marked degree of kyphosis, the ribs are thickened and their curvature increased, but the pelvis is usually only slightly affected. The blood-phosphatase is increased, the blood-calcium and phosphorus are normal and no specific changes have been found in any of the endocrine glands. Osteogenic sarcomas are sometimes associated with and probably developed as a sequel of this condition.

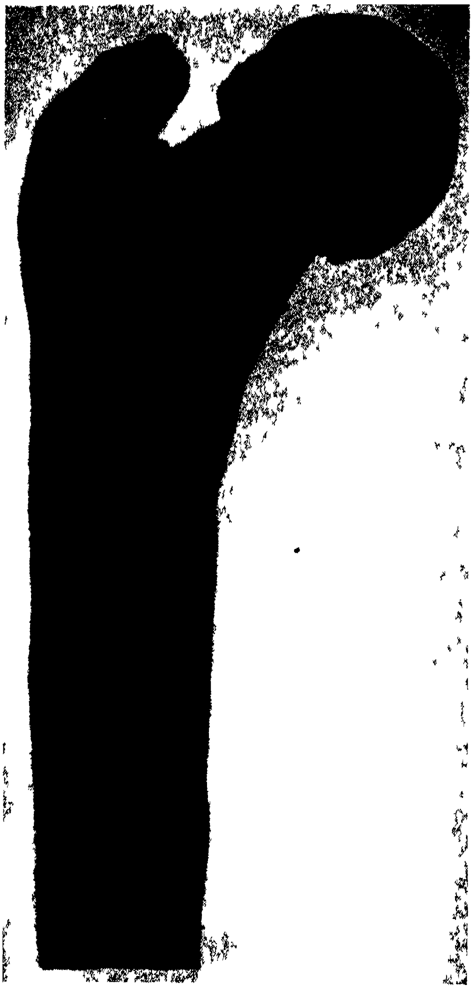


FIG. 780. *Osteitis Fibrosa of the Femur.* Note widening of the medullary cavity, and the formation of cystic spaces in the marrow.

On microscopical examination, the histological picture is variable. There is increase of finely porous cancellous bone with very irregular lamellæ alternating with foci of fully-formed unaffected bone and fibrous tissue. This alternation suggests the mosaic appearance referred to by Schmorl. Absorption and ossification go on side by side and in the areas of absorption osteoclasts are abundant. On previously-rarefied trabeculæ, new layers of bone are often seen and some areas show the development of fibrous tissue in the marrow-spaces.

2. "**Osteitis Fibrosa.**" Two distinct diseases of bone have been described under this term. One is a focal, and the other a generalised, condition.

(*a*) **Focal Osteitis Fibrosa.** This is frequent in childhood and youth and consists of a local loss of bone and its replacement by fibrous tissue. The disease occurs as a rule in the long bones at the extremity of the diaphysis. Pseudocyst-formation and the development of giant-celled tumours are common. The local rarefactions are due to trauma, hæmorrhage or irregularities in bone-formation and are in no way related to hyperparathyroidism. The blood-calcium and the blood-phosphatase are normal.

(*b*) **Generalised Osteitis Fibrosa et Cystica** ("von Recklinghausen's disease of bone" [1]). This disease is due to overactivity of the parathyroids—**hyperparathyroidism** (p. 837 *et seq.*), and the usual cause is hyperplasia or tumour-growth in one or more of these glands. Most of the bones are affected, though in varying degree. The most pronounced changes occur in the humerus, femur and tibia, but the vertebræ, ribs and skull may show similar pathological lesions. The bones of the skull may be much thickened, but they are porous and, if water is poured into the macerated skull-cap, the bone acts as a "filter." The bones become soft, often pliable like leather, and are easily cut with a knife. Owing to these changes, bending and extreme deformities of the long bones and spine occur. Fractures are common, and pseudo-cysts are formed, with either clear or more frequently with red gelatinous contents. Microscopically, the contents of these pseudo-cysts usually show a mixture of blood-corpuscles, fibroblasts and giant-cells. The lesions result from the decalcification and resorption of existing bone, and its replacement by an osteoid and fibrous matrix in which inefficient attempts at calcification take place. There is an excess of calcium in the blood and a diminution of phosphorus, with excessive excretion of these in the urine. The blood-phosphatase is raised. The marrow also undergoes fibrous change. Metastatic calcification occurs in the walls of the arteries and in the lungs, kidney and stomach. The development of giant-celled tumours—osteoclastomas (pp. 308 and 1227)—is not uncommon and, by some authors, is regarded as a characteristic feature of the disease. Removal of the parathyroid tumour will arrest the disease and allow the resumption of normal calcification. The deformities persist, but the rarefied osteoid tissue becomes consolidated.

Experimentally, the giving of an excess of parathyroid hormone ("parathormone") to animals has led to the production of alterations in calcium-metabolism and in bone-formation analogous to those occurring in this disease. Similar changes have been produced in human cases by its prolonged over-administration therapeutically.

3. **Osteomalacia,** or "softening of bone," is a disease found in women, generally during the child-bearing period, though it has been described as occurring at puberty and after the menopause. It is relatively commoner among the poor and ill-nourished, particularly in the East, especially in India and China, and in some European countries after the War of 1914–18 as so-called "hunger-osteopathy." Unduly frequent child-bearing plays an important part in its causation. It is due to a deficiency in vitamin D and in calcium-intake and/or in their absorption and utilisation (p. 440), though bad hygienic conditions, poor food, and lack of sunlight are important associated factors. The parathyroids may show hyperplasia, but this is regarded as an effect rather than a cause. Osteoid tissue is formed, but it does not become calcified because of the absence of vitamin D. Further, it must be remembered that there is a special need for calcium in the development of the fœtus, with a consequent drain on the calcium of the bones of the mother, and in many cases deficient calcium-intake in the food. In its early stages, it

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[1] Not to be confused with multiple peripheral neurofibromatosis, often called "von Recklinghausen's disease" (pp. 301 and 1135 *et seq.*).

affects especially the bones of the pelvis, but, later, the disease may spread to the vertebræ, the ribs, and the femora. The bones of the head, and those of the hands and feet, are implicated only in very exceptional cases. The affected bones are so soft that they can be readily cut with a knife ; and bending of them, wherever pressure is exerted, is a common result. In the pelvis (Fig. 781), the bones become compressed or pushed inwards at the acetabula—*i.e.*, along the lines of pressure which pass through the heads of the femora—as well as at the sacrum, through which the weight of the body is communicated. The symphysis pubis is pushed forward, and forms a beak-like projection ; and the anterior surface of the sacrum shows an increased concavity, its promontory being carried forward. The cavity of the pelvis is thus narrowed, and the pelvic inlet becomes heart-shaped or tri-radiate. From the character of these distortions, the pelvis has been termed the " crushed " or " beaked " pelvis. The femora, and the other long bones of the lower limbs, may show marked bending ; and, if the vertebræ are softened, curvature and twisting of the spine in various directions take place. The ribs soften, and so-called " spontaneous " fracture occurs, the lateral diameter of the chest being narrowed and its antero-posterior diameter increased.

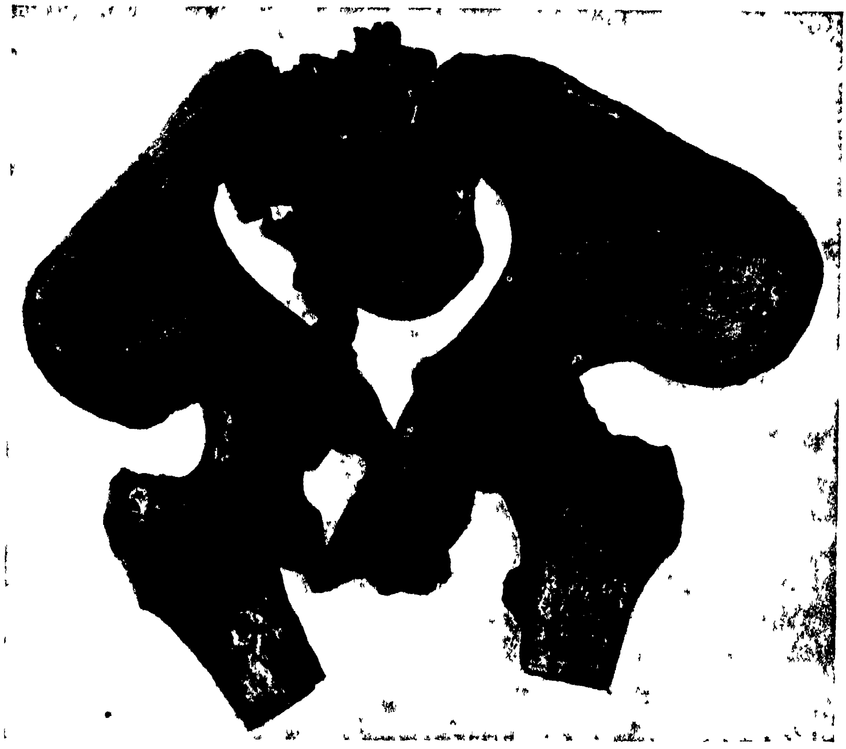

FIG. 781. " *Crushed Pelvis* " *:* from a case of osteomalacia.

An analogous condition of the bones has occasionally been recorded in the male, *e.g.*, in a man who had taken Carlsbad salts daily for a period of thirty-five years.[1]

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[1] For a recent review of the subject, see "Osteomalacia: The Known Factors," editorial article, *Brit. Med. Jour.*, 1940, i, 352.

Changes in the Affected Bones. There is decalcification of the bony trabeculæ near the medullary spaces and the Haversian canals—this process gradually extending towards the surface. Associated with the decalcification, absorption and atrophy of the trabeculæ occur, and thus the medullary spaces are increased in size. These changes are usually very irregularly distributed. The decalcification commences at the surfaces of the trabeculæ, often leaving the central part ossified.

In the advanced stages of the disease, there may be merely a thin external layer of bone, surrounding very spongy tissue, in which calcareous salts may be left only in very few areas. The " bone-marrow," or at all events the tissue contained in the marrow-spaces in the bones, shows usually a great increase in its cellular elements, the large osteoclasts or multinucleated giant-cells being specially abundant ; and hæmorrhages are not uncommon.

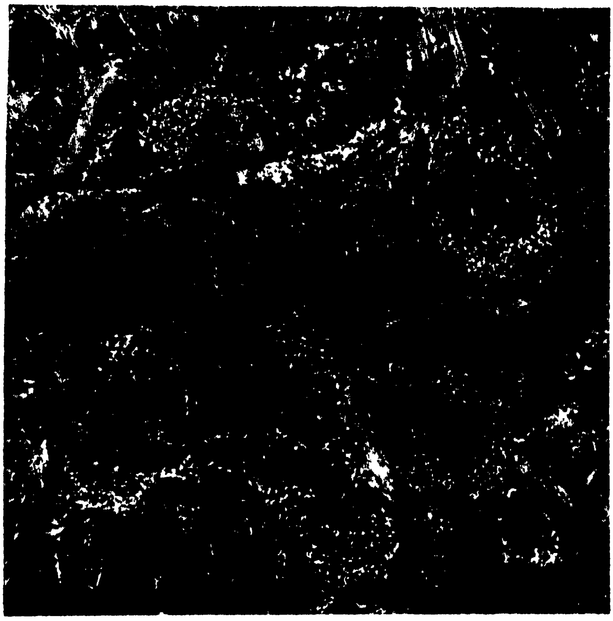

FIG. 782. *Section o a Vertebral Body in Osteomalacia :* showing widening of the medullary spaces, with absorption of the bony trabeculæ. × 60.

(4) **Achondroplasia.** In this congenital disease, which is generally regarded as due to the presence of some unknown endocrine disorder, the growth of those bones which are formed in cartilage is deficient. The epiphyses of the long bones are enlarged, but the diaphyses " shortened," *i.e.*, there is deficient elongation, the shortness of the bones being caused by a failure of activity of the epiphyseal cartilage. The base of the skull is proportionately diminutive and the frontal region bulges unduly. The mandible is usually prominent and the bridge of the nose depressed. All these changes are due to imperfect ossification in cartilage, whilst membranous ossification is *not* deficient. The disease thus results in the production of dwarfs with a normal-sized trunk, short arms and legs, large head and depressed bridge of the nose. **Microscopically,** the rows of cartilage-cells in the epiphyseal line are irregular, and the cells enlarged, with little evidence of proliferation and no ossification.

(5) **Osteogenesis Imperfecta or Fragilitas Ossium** develops usually during intra-uterine life and is characterised by undue fragility of the bones with deficient ossification.

" Spontaneous " fractures may occur in several situations, perhaps at the same time, from trivial violence. The ossification of the skull may be so imperfect that it is represented by a membrane with a few bony plates. The cartilage-cells of the epiphyses proliferate as in normal development, but the amount of bone formed is very limited. The ætiology of the disease is unknown, but a common view is that it is an endocrine disorder. In cases of osteomalacia of the mother, the bones of the fœtus may be soft, fragile and deficient in calcium. One variety of osteogenesis imperfecta in which fractures are not so common is said to be hereditary and familial. Blue sclerotics are often associated with the non-familial type.

(6) **Chronic Hypertrophic Pulmonary Osteo-arthropathy** is usually associated with pulmonary diseases such as bronchiectasis, chronic phthisis, and empyema, and, less commonly, with congenital heart-disease. There is subperiosteal thickening of the bones of the hands and feet and, to a lesser extent, of the lower parts of the leg and forearm. Thickening of the soft tissues of all four limbs, and especially of the tips of the fingers, producing " clubbing," is often present. The nails are thickened and convex, and there is overgrowth of the soft tissues under the nail-bed. The changes are probably caused, at all events in part, by congestion and œdema associated with imperfect oxygenation of the blood. Similar clubbing, but without evidence of these changes in the bones, is seen in subacute infective endocarditis (p. 456).

Rickets. This is a deficiency-disease of children and develops during the first two years of extra-uterine life. It is caused principally, if not wholly, by improper feeding and bad hygienic surroundings, especially want of sunshine. The primary defect is lack of vitamin D, aided by deficiency in the supplies of calcium and phosphorus. Vitamin D (p. 440) facilitates the absorption of calcium and phosphorus from the intestine and its utilisation by the tissues. When the vitamin is absent, or present only in inadequate amount, absorption of calcium and phosphorus from the bowel is deficient and there is, in consequence, a lack of these essential food-elements and a failure to reach their normal level in the blood. As a result, the bone-matrix, even if it has an adequate supply of phosphatase, cannot obtain sufficient calcium and phosphorus for its efficient ossification and it therefore remains soft and imperfectly calcified. As rickets is essentially a disease of the early growth-period, the bone and cartilage increase in size, but develop in such a way that an excess of osteoid tissue is produced. If the normal calcium-phosphorus balance is restored by the administration of vitamin D, calcification takes place and the disease is arrested. Further, it has been shown that the occurrence of rickets may be prevented by ultra-violet radiation, even in the absence of vitamin D in the food—the vitamin being synthesised from the inactive ergosterol in the skin by the radiation. Calciferol has been separated from irradiated ergosterol in crystalline form, and is anti-rachitic. **Tetany** (pp. 837–8), which is common in cases of rickets, is due to a low calcium-content of the blood-serum, and resulting increased irritability at the neuro-muscular junctions.

Morbid Anatomy. Deformities, not only in the shape of the bones, but also in their histological structure, are characteristic of rickets. These changes are due partly to absorption, and partly to irregular but excessive growth. There is **enlargement** of the ends of the long bones, especially at and near the cartilaginous zone between the ossifying epiphysis and shaft : **thickening** of the flat bones, *e.g.*, the scapula, pelvis and skull : **softening** of all the bones : and **deformities** of the softened bones, produced usually by mechanical pressure. This abnormal enlargement of the ends of the long bones is seen best at the junction of the ribs with the costal cartilages (Fig. 783), producing the characteristic "beading" of the ribs—and at the lower ends of the radius and ulna. It may, however, be present at the growing ends of any of the long bones. The enlargement is due to an excessive activity of the processes which precede ossification, to an irregularity in the method of bone-formation, and to a retardation of the process. There is an abnormal increase in the amount of spongy tissue ; the bone in which the irregular ossification is taking place is much more vascular than normal ; and reddish, vascular areas may also be seen in the cartilage. The blue line of cartilage which marks the junction of the epiphysis with the shaft of the bone is usually very irregular, considerably increased in thickness, and in marked contrast with the uniform, well-defined narrow line seen in normal ossification. The flat bones become thickened, and the "clubbing" of the lower ends of the long bones tends to persist in later life, though in many cases it ultimately disappears. The soft and spongy character of the bone during the active progress of the disease leads to bending and the production of various deformities, which often persist when the bones become denser and firmer, as they do when the active period of the disease passes off. In the long bones, the deformities occur especially in the lower limbs and take the form of curvatures, the two principal forms of which are **genu valgum** and **genu varum** (p. 1217).

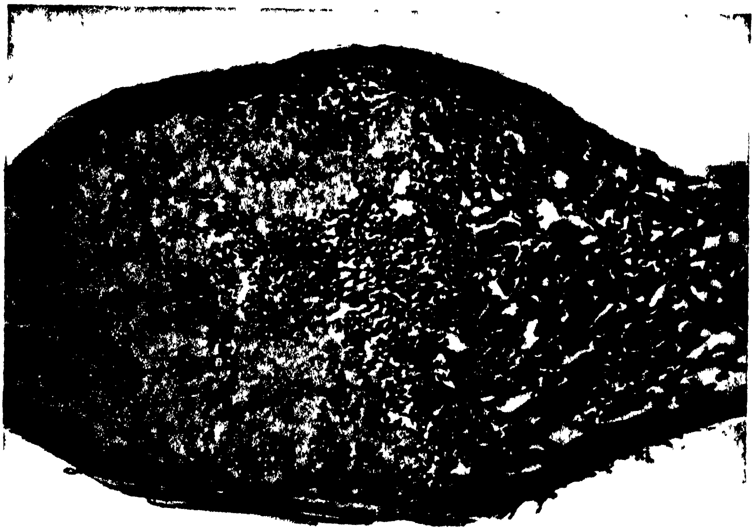

FIG. 783. *Rickets : Longitudinal Section of the Costo-chondral Junction,* showing a very extensive and irregular line of ossification. × 5.

On microscopical examination, there is considerable increase in the breadth of the zone of multiplying cartilage-cells. The cells are more numerous and are arranged in rows which are less regular than those of normal ossifying tissue. The individual cells may be swollen, or may be smaller than normal—such variation in size being a conspicuous feature. Calcification of the matrix and of the cartilage-cells, is also irregular, some of the calcified cells lying close to the line of ossification, others being situated at considerable distances from it. Sometimes, the cytoplasm of the cartilage-cells calcifies, whilst the nucleus remains unaltered. This irregular calcification of the cells may take place close to, and be continuous with, the bone, the uncalcified nucleus resembling a bone-corpuscle, its appear-

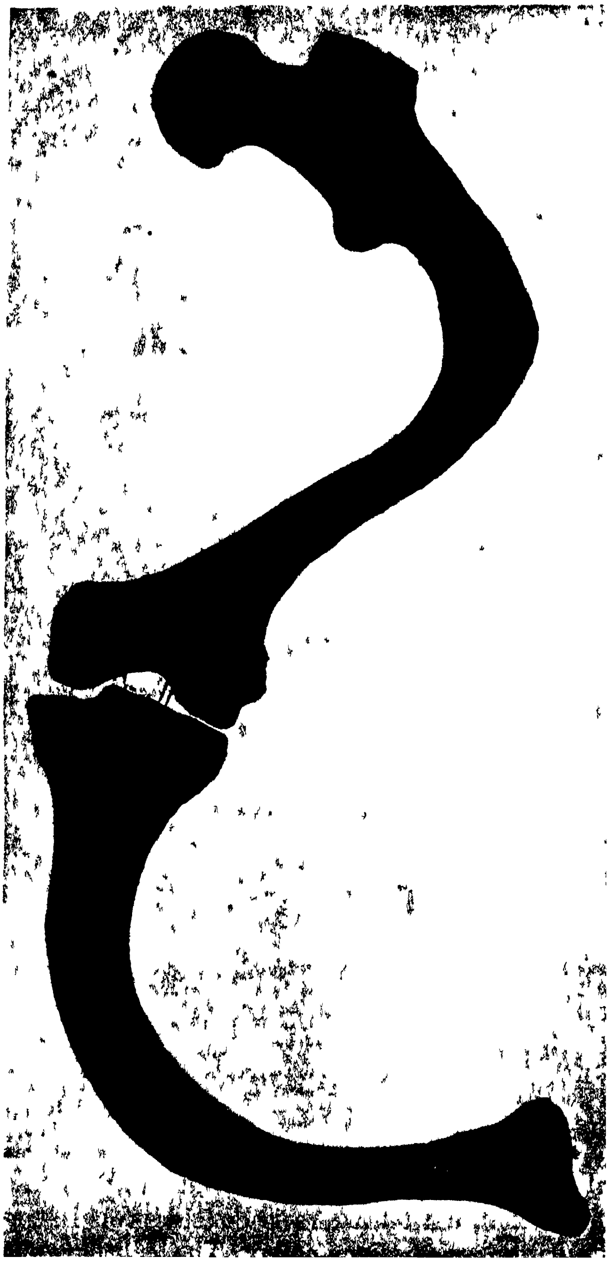

FIG. 784. *Extreme Rickety Deformities of the Femur and the Tibia.* (These were the bones of David Ritchie ("Bowed Davie"), Sir Walter Scott's "Black Dwarf."[1]) Note the flattening of the shafts of the deformed bones. (Edinburgh University Anatomical Museum.)

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[1] See Dr. John Brown's essay, in his "*Horæ Subsecivæ*". Second Series, on "The Black Dwarf's Bones"—which in the book immediately precedes that Author's little masterpiece of medical history and literature, "Rab and His Friends."

ance suggesting the possible transformation of cartilage-cells into bone-corpuscles. Blood-vessels are seen in the midst of the cartilage, having penetrated from the bone—hyaline cartilage being, under normal circumstances, a non-vascular tissue—and, around the vessels, absorption and ossification may be taking place simultaneously. In the osteogenic layer of the periosteum, an excessive formation of cells and an increased vascularity occur, and the osteoblasts may form a layer of considerable thickness. Bone may be formed in excessive amount, but is usually spongy in character, imperfectly developed, and, as a general rule, unduly vascular. The matrix is granular, the lime-salts being deposited in an irregular fashion, and true bone is not formed. Thus, the process is really one of imperfect calcification rather than ossification, and the new tissue has been described as " osteoid " tissue.

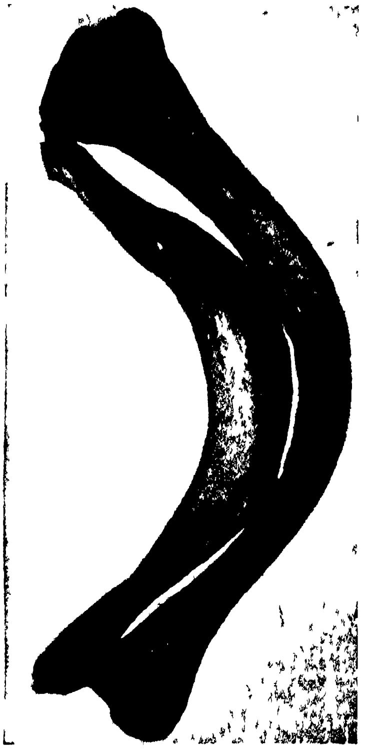

Fig. 785. *Rickety Deformities of Tibia and Fibula.* Note the flattening of the bones – especially of the fibula – and the sickle-shaped margin.

In **Genu valgum,** or **knock-knee,** there is usually a curving of the lower part of the femur —the convexity of the curve being inwards. Thus, the internal condyles of the femora are thrown together, and are placed at a lower level than those on the outer sides. The tibiæ diverge from one another, but are not necessarily curved. The femur may, in addition, show an anterior curvature, and the tibia a similar condition. In an advanced stage of the deformity, the knee-joints may cross each other.

In **Genu varum,** or **bow-legs,** the shafts of both the femora and the tibiæ are curved—the convexity of the curve being outwards. The tibia usually shows the condition in much more marked degree than the femur. Anterior curvature may also be present.

Deformities in the bones of the arms are not so common or so pronounced. Partial or complete fracture of the long bones is—on account of their softness—liable to occur in the earlier stage of the disease. In the incomplete or "greenstick-fracture," the convex surface of the bone gives way, but the concave does not.

In the chest, the deformity may be marked, and its effects serious. Besides the " beaded " appearance of the ribs, to which reference has already been made, there may be, during inspiration, and while the bones are still soft and yielding, a drawing-in of the ribs, and the production of a depression which runs transversely from the lower end of the sternum across the chest, on each side, to the posterior margin of the axilla, about the level of the diaphragm. Another depression is produced which runs obliquely down the anterior aspect of the chest on each side, along the line of junction of the bony ribs with the costal cartilages. It is in the line of this latter depression that the " beading " of the ribs is seen, the so-called "rickety rosary." These changes cause a straightening of the ribs, with a consequent pushing forward and bending of the sternum and give rise to the "pigeon-breast" appearance. The deformities thus produced may interfere with the respiratory movements and seriously complicate acute or chronic diseases of the lungs.

The softening of the vertebræ may produce an exaggeration of the normal antero-posterior curvature or even be the cause of lateral curvature. The spinal curvatures tend to produce corresponding deformities of the thorax and abdomen, and displacements and other abnormalities in their contents. The chief deformity in the pelvis is a pushing forward of the promontory of the sacrum, and a consequent diminution in the antero-posterior diameter of the inlet—a condition usually associated with exaggeration of the lumbar convexity. In the skull, the bones may be thickened, the circumference of the cranium increased, and the summit flattened, so that the frontal eminences bulge, and, in severe cases, the forehead may come to overhang the face. The parietal eminences may also be unduly prominent, and produce—along with the protuberant frontal bones—the square or box-shaped cranium. The closure of the fontanelles is usually delayed. The teeth erupt irregularly and the enamel and dentine are thin and imperfectly calcified. **Craniotabes** is sometimes associated with rickets, but is really a manifestation of congenital syphilis (pp. 83–4).

In rickets, recovery from the active disease may take place, but, usually, varying degrees of deformity persist. A reparative process frequently supervenes, and a definite sickle-shaped ridge (Figs. 784–5) is produced along the concavity of the shafts of the deformed long bones. This acts as a buttress, and may considerably strengthen the bones, which, in after life, not infrequently become abnormally dense in texture. It is common to find, in association with rickets, enlargement of the liver and spleen, dilatation of the stomach, enlargement of mediastinal lymph-nodes and gastro-enteritis.

Renal Rickets. This condition occurs in older children or in adolescents. The changes in the bones are similar to those described under rickets, but, in addition, there is often stunting of growth—renal infantilism and renal dwarfism. The primary lesion is in the kidney—usually a chronic nephritis with failure of renal excretion and acidosis. The calcium-metabolism is disturbed either by a removal or a non-utilisation of the calcium, but there is no association with deficiency of vitamin D.

Infantile Scurvy—Barlow's Disease. This disease, which has been called scurvy-rickets, is essentially a scorbutic manifestation in a rickety child, and is due to a deficiency of vitamin C (pp. 442–4). Hæmorrhagic extravasations are common, and are found in the subperiosteal tissues of the tibia and femur near the joints. Occasionally, the epiphysis becomes separated. Hæmorrhages into the skin and subcutaneous tissues and the gums and from the mouth, nose, bowel and kidney may occur. The periosteum of the affected bone becomes thickened and unduly vascular, and the underlying bone rarefied. New subperiosteal bone may be formed, but this is always imperfect. There is often, but not invariably, an associated anæmia, due partly to the loss of blood from these hæmorrhages and partly to the causal vitamin-deficiency itself.

Tetany. Infantile tetany is commonly associated with rickets (p. 1214). The calcium-phosphorus balance is disturbed. The serum-calcium is lowered because, owing to deficiency of vitamin D (p. 440), the absorption of calcium from the intestine is imperfect (p. 837). The condition is characterised by a heightened excitability of the motor-nerves and nerve-endings with resulting spasms, especially of the muscles of the lower limbs.

TUBERCULOSIS and SYPHILIS of BONE. These are described in Chapter III, pp. 66 and 83.

CURVATURE OF THE SPINE :—

(*a*) **"Angular curvature,"** described by Percival Pott in 1779, and hence often called "Pott's disease," is due most frequently to a local tuberculosis of the bodies of the vertebræ (pp. 66 to 68), which, as they become softened and eroded by the disease, give way and become compressed by the weight of the body, whilst the unaffected neural arches bulge backwards, producing a definite, more or less prominent, angle. The spinal cord is frequently crushed (Fig. 600, p. 999), the conducting fibres being interrupted, but rarely involved in the direct spread of the tuberculosis. A similar deformity of the spine may be produced by collapse of the vertebral bodies when these are the seat of malignant disease, *e.g.*, secondary invasion from carcinoma of the breast (Fig. 732, p. 1145) or prostate (Fig. 542, p. 914).

(*b*) **Kyphosis**[1] is a deformity in which there is increased convexity of the spine backwards, generally most prominent in the dorsal region and due to defective bone-formation and muscular weakness. It is therefore often associated with rickets, osteitis deformans, osteitis fibrosa, acromegaly (Fig. 464 (A), p. 812) and with some forms of tumour-growth, *e.g.*, multiple myeloma, (Fig. 153, p. 320), in which the spine is extensively invaded.

In a minor degree the condition is seen in cases of emphysema.

Adolescent kyphosis is an important variety of spinal curvature which attacks especially boys during the age-period twelve to seventeen years—at which the vertebral epiphyses appear, and some writers attribute it to interference with normal ossification by a severe trauma or a series of minor traumata. Degeneration with consequent narrowing of the intervertebral disks occurs, and a permanent kyphosis, with wedge-shaped vertebral bodies, supervenes. It is not infrequently associated with the appearance of Schmorl's nodes, *i.e.*, herniations of the nucleus pulposus[2] into the vertebral bodies (Fig. 786, p. 1220), and also with what have in the past sometimes been erroneously described as "chondromas" of the intervertebral disks. Such bulgings or herniations may take place into the spinal canal, and may lead to compression of the cord. Schmorl found such projections in about 15 per cent. of his routine post-mortems, and Elsberg found such nodules (which he took to be chondromas) in 14 out of 100 cases of tumours of the spinal cord. They are non-neoplastic, but clinically the symptoms produced may simulate those of a slow-growing, spinal-cord tumour, or of some "osteo-arthritic" condition. As stated by Geoffrey Jefferson (1936) in a review of the Surgery of the Spine and Spinal Cord, this "new pathological entity deserves wide recognition." (*See* p. 1220 *et seq.*).

[1] These Greek terms were used by Hippocrates and Galen :—

κύφωσις, kuphōsis or kyphōsis, from *κυφός, kuphos*, bent forward, stooping, hump-backed, and *κῖφος*, a hump.

λόρδωσις, lordōsis, from *λορδός, lordos*, bent backward so that the spine is convex in front and the head thrown back.

σκολίωσις, skoliōsis, from *σκολιός, skolios*, bent sideways or twisted.

[2] "Herniation of the Nucleus Pulposus producing Compression of the Spinal Cord (complicated by Chronic Staphylococcal Granuloma," Carnegie Dickson, *Proc. Roy. Soc. Mea.* (Section of Neurology), London, 1936, **29**, 61–69.

(c) ***Lordosis***[1] *is usually confined to the lumbar region, where it constitutes an exaggeration of the normal lumbar convexity. It is generally a manifestation of rickets, though it occurs also in congenital dislocation and in ankylosis of the hip. The convexity of the curve is forwards.*

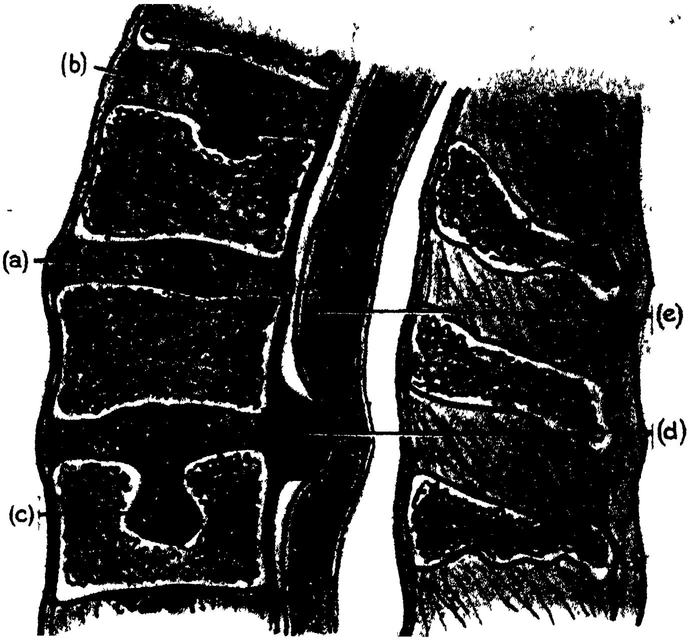

FIG. 786. Mesial vertical section: diagrammatic representation of the *formation of Schmorl's nodes* in the vertebral bodies and *herniation of a nucleus pulposus* backwards into the spinal canal, producing compression of the cord (after Schmorl). (a) *Nucleus pulposus*; (b) *nucleus pulposus* with slight invasion of the vertebral body below; (c) *Schmorl's node*; (d) *herniation of nucleus pulposus* into spinal canal; (e) *spinal cord.* (Compare Fig. 790.)

(*d*). **Scoliosis**[1] **or Lateral or Rotato-lateral Curvature**:—

In this condition, there is a lateral deviation, with a partial rotation of the vertebræ. This may develop in rickets, or, in its milder forms, merely as the result of a bad habit in standing or sitting. Lateral curvature, of necessity, produces corresponding deformities of the chest and shoulder-girdle, and also of the abdomen and pelvis, together with displacements and other abnormalities of internal organs. One of its most serious results is extensive collapse of the lung.

PROLAPSED INTERVERTEBRAL DISKS ("**Herniation of the nucleus pulposus**": "**Rupture of the intervertebral disk** with extrusion of the nucleus pulposus": "**Slipped disk**"):—

The fibro-cartilaginous plate or intervertebral disk between each two vertebral bodies consists of the **nucleus pulposus,** a semi-fluid substance situated in the central part of the disk: and an outer enclosing spherical elastic structure, the **annulus fibrosus.** Under conditions of normal stress, the cushion-

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[1] *See* note, p. 1219.

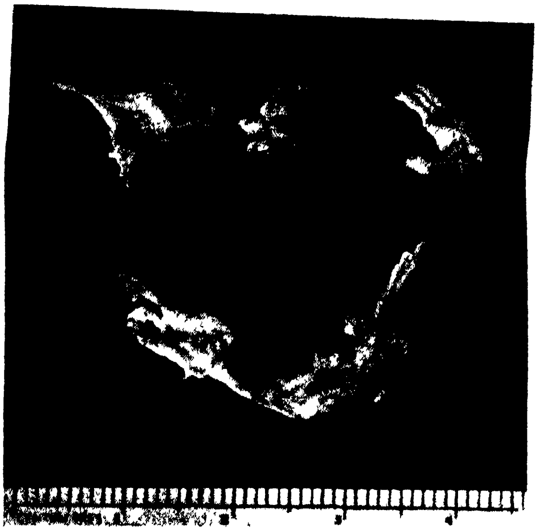
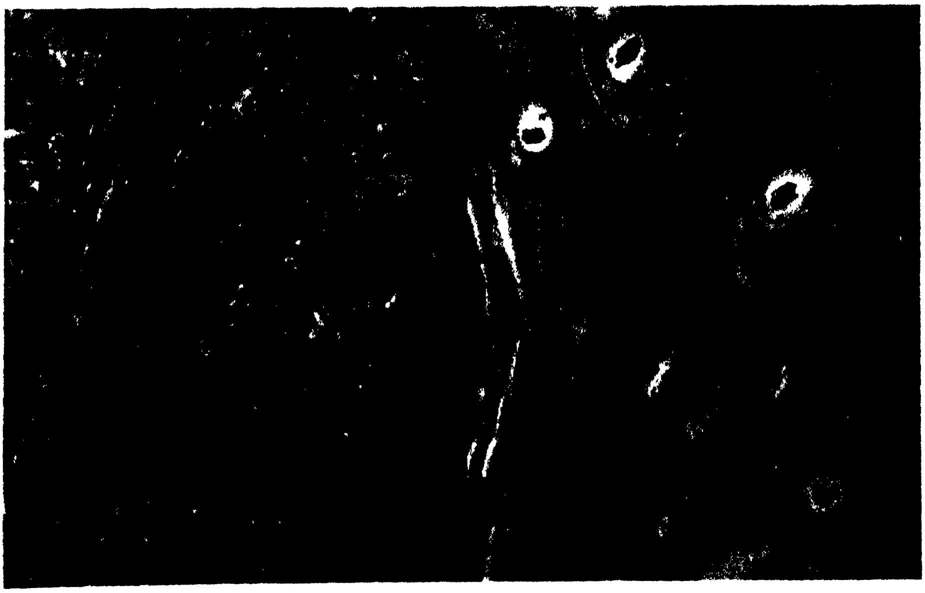


FIG. 787. *Fragments of Herniated Intervertebral Disk* between fifth lumbar and first sacral vertebræ, removed by operation in a man aged fifty-eight. The projection of the disk into the vertebral canal had caused intractable low backache and sciatica from which there was immediate and lasting relief after the removal of the herniated portion of the disk by Mr. Geoffrey Knight. (W.E.H. case.)

like disk protrudes slightly, but retracts to its normal position as soon as the stress ceases. The anterior and posterior longitudinal ligaments which support the spinal column keep the disks in position (Figs. 786 and 790).

Grafton Love, of the Mayo Clinic (1939), from the examination of 300 proved cases, concludes that a history of trauma to the back, especially from the



(A) × 85. (B) × 350.

FIG. 788. *Herniation of an Intervertebral Disk :* low- and high-power photomicrographs of a section of one of the fragments of fibro-cartilage shown in the preceding Fig. 787. (Mallory's connective-tissue stain.)

lifting of heavy weights, frequently precedes the onset of symptoms—sometimes one outstanding injury, but more frequently repeated traumata with aggravation or recurrence of previous pain. He suggests that the original injury may have weakened the longitudinal spinal ligaments and the annulus fibrosus without protrusion of the disk, and that a subsequent injury, less severe than the previous one, has produced the actual herniation. The most characteristic symptoms are pain in the distribution of one or more nerve-roots.

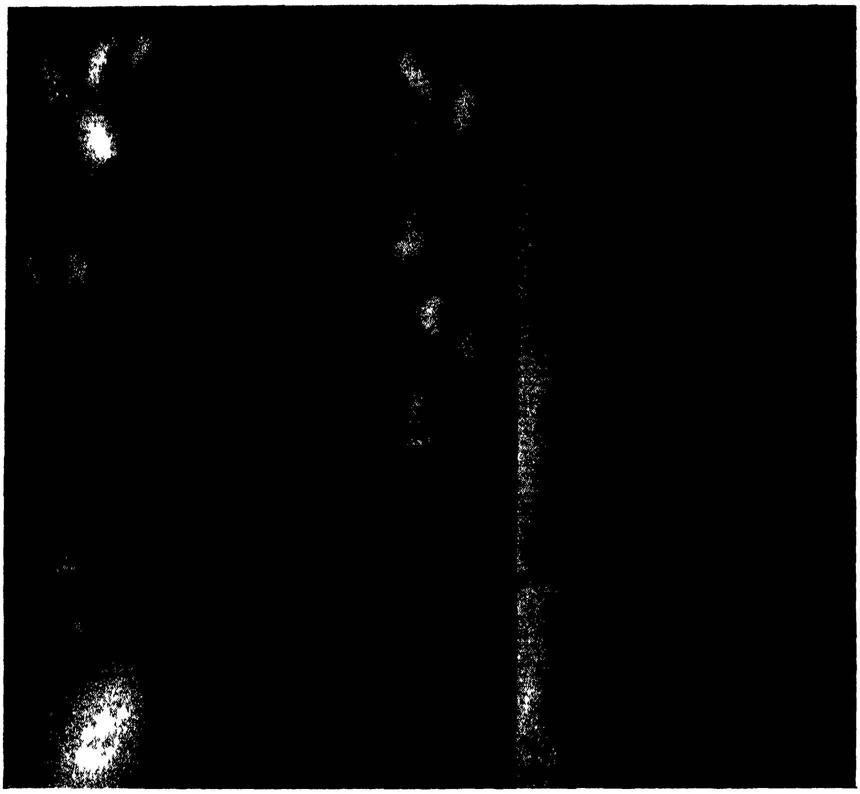
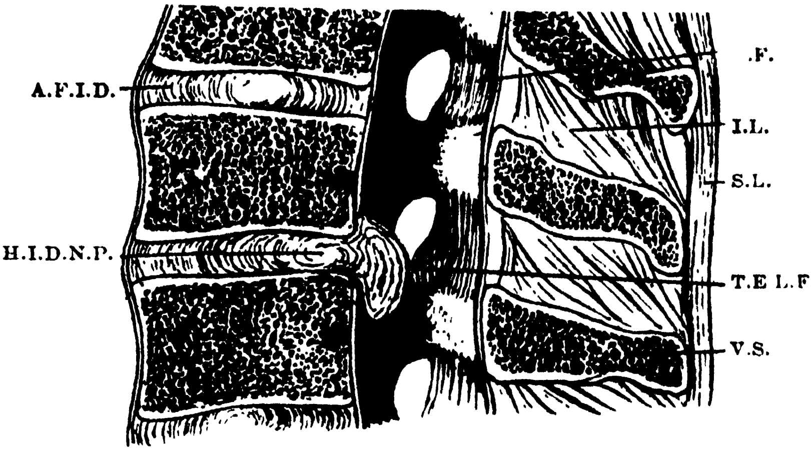

(A) (B)

FIG. 789. *Prolapsed Intervertebral Disk :* (A) Antero-posterior and (B) lateral oblique X-ray photographs (reduced × ½ approx.) of a case of prolapse or herniation of the lowest lumbar intervertebral disk, causing pressure on the nerve-roots (*cf.* Fig. 790). The break in the lipiodol injected into the theca indicates the position of the projecting disk which had caused persistent " sciatica " for many years—completely cured by surgical removal of the prolapsed portion of the disk (*cf.* Figs. 787–8). (W.E.H. case.)

The majority of protrusions take place in the lumbar region (especially between L.4 and 5, or between L.5 and S.1) and the pain therefore is low down in the back and in the region of the sciatic nerve and its distribution. It may be centred in the lumbo-sacral junction and is usually accentuated by coughing, straining at stool, or any other action which increases the intraspinal pressure. Spasm of the lumbar muscles causes all movements of the back to be limited and painful. Concerning the pathological findings, it is stated that posterior protrusions causing clinical symptoms that justify operation are composed of both the annulus fibrosus and the nucleus pulposus, with occasional remnants of the embryonic notocord. There are structural alterations in the architecture of the disk. Degeneration of the cartilage-cells is much more frequent than degeneration of the fibrils ; fibrous tissue tends to replace the normal fibro-cartilaginous structure of the disk, and œdematous swelling of the protruded part is common.

FIBROTIC THICKENING OF LIGAMENTA FLAVA. Other writers,[1] mostly in America, have recorded cases of "**low back-pain and sciatica**" caused by the local **thickening of one of the ligamenta flava** (subflava), the yellow elastic ligaments which fill up the interspaces between upper and lower margins respectively of the laminæ of the neural arches of successive vertebræ (Fig. 790). The antero-external edge of each ligamentum flavum forms the posterior margin of the corresponding intervertebral foramen through which a spinal nerve leaves the vertebral canal, the anterior margin being formed by the side of the anterior surface of the corresponding intervertebral disk. Pathological thickening of one of these yellow ligaments sometimes follows some injury, probably in most cases a partial rupture (with or without accompanying damage to the bony lamina itself), the occurrence of such damage being, like herniation of an intervertebral disk, most liable to take place **between the fourth and fifth lumbar,** or between the fifth lumbar and first sacral vertebræ. Either or both boundaries of an intervertebral foramen may thus come to be the seat of swellings which bulge into the main spinal canal and at the same time may encroach upon the foramen and cause compression of the emerging spinal nerve. The lesions of both disk and



A.F.I.D. = Annulus fibrosus of intervertebral disk.
H.I.D.N.P. = Herniation of intervertebral disk and its nucleus pulposus.
L.F. = Ligamentum flavum.
I.L. = Interspinous ligament.
S.L. = Supraspinous ligament.
T.E.L.F. = Thickened edge of ligamentum flavum.
V.S. = Vertebral spine.

(Modified from "Cunningham's Anatomy," by kind permission of the publishers.)

FIG. 790. Median section through part of the lumbar spine, showing narrowing of an intervertebral foramen between the thickened edge of a ligamentum flavum and a herniated intervertebral disk.

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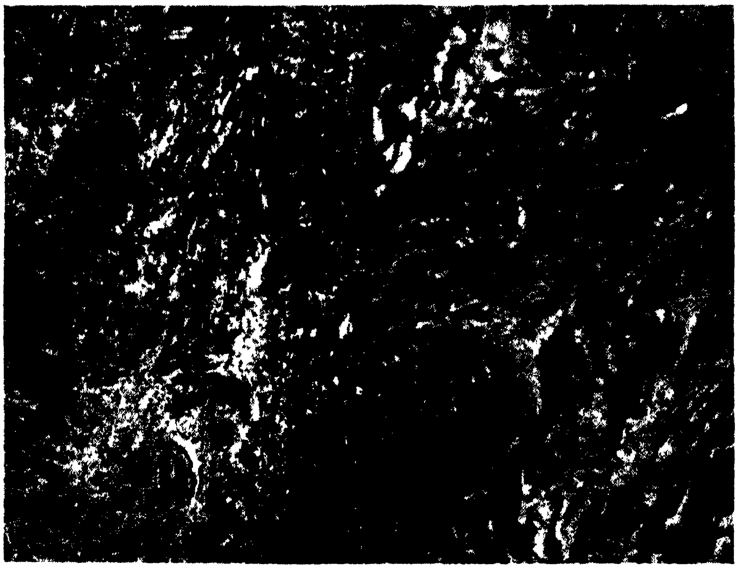
[1] *See* E. W. Hey Groves, "Low Backache and Sciatica," "Ruptured Intervertebral Disk," and "Thickened Ligamenta Flava," in his review on "Surgery of the Spine," *Medical Annual,* 1939, 462: and "Sciatica, Low Back Pain, and the Intervertebral Disk," leading article, *Brit. Med. Jour.,* 1940, ii, 708.

(1) (2)

FIG. 791. *Thickened Ligamentum Flavum as a cause of Low Back-Ache Pain and Sciatica* (*see* text opposite).

Longitudinal section of an almost intact portion of ligamentum flavum. (Mallory's connective-tissue stain.) × 100.

Section of two small round fibrous scars, with darn-like repairs. (Verhoeff.) × 100.



(3) FIG. 791 (*continued*). (4)

Longitudinal section of the margin of the main area of hyperplastic scar-tissue. (Verhoeff.) × 100.

Higher magnification of section shown in (3) at edge of scar, showing thick fragmented fibres and thin wisps of degenerating fibres. (Verhoeff.) × 400.

(W.E.H. case. Reproduced by kind permission of the Editors of the *Lancet*.)

ligament, if as sometimes happens they occur together, may have been brought about by the same injury, for example their rupture whilst the patient was lifting a heavy weight (*see* preceding paragraph). In Fig. 791 are shown the details of the formation of scar-tissue following upon an old injury, leading to considerable thickening of both lateral components of the yellow elastic ligament between the neural arches of the fourth and fifth lumbar vertebræ, and causing symptoms of compression of the cauda equira. In this case, surgical removal of the greatly thickened ligament by Mr. Geoffrey Knight gave immediate relief.[1]

TUMOURS OF BONE :—

The following is the revised classification adopted by the Committee of the American College of Surgeons in 1939 :—

	Malignant	*Benign*
1. Osteogenic series	*a.* Medullary and subperiosteal.	Exostosis.
	b. Telangiectatic.	Osteoma.
	c. Sclerosing.	
	d. Periosteal.	
	e. Fibrosarcoma, medullary, subperiosteal.	
2. Chondroma series	*a.* Chondrosarcoma.	Chondroma.
	b. Myxosarcoma.	
3. Giant-cell tumours	*a.* " Benign " (so-called) : and malignant.	Epiphyseal giant-celled tumour.
4. Angioma series	*a.* Angio-endothelioma.	Cavernous angioma.
	b. Diffuse endothelioma.	Plexiform angioma.
5. Myeloma series	*a.* Plasma-cell.	
	b. Myelocytoma.	
	c. Erythroblastoma.	
	d. Lymphocytoma.	
6. Reticulum-celled sarcoma.		
7. Liposarcoma.		

For convenience of study, we suggest that giant-celled tumours should be dealt with in a group by themselves, and we therefore propose to describe the tumours of bone in three groups.

Group I. Benign Tumours. To this group we add **fibromas** (p. 298), which, though rare, may develop from the periosteum and exhibit areas of calcification, chondrification and sometimes of fully-developed bone. **Chondromas** (p. 303) may grow on the surface or in the interior of bones, and the latter (**Enchondromas**) may cause expansion of the shaft, and in radiographs may simulate giant-celled tumours. They arise from epiphyseal or other cartilages, or from islets of cartilage which have not been completely ossified or which remain unabsorbed (Figs. 135–6, p. 304). They often show myxomatous degeneration, which produces localised softening, and even the formation of cyst-like cavities—the so-called "cystic" chondroma. In some instances, they undergo more or less imperfect ossification. They may be multiple and are commonest in the short bones of the hands and feet, but occur also in the scapula and humerus. They may acquire malignant properties and as **chondro-sarcomas** invade the bones, enter into the veins or lymphatics and produce metastases. The actively growing area in these tumours is probably the cap of cells at the periphery. **Myxo-sarcomas** are described, but some at least of these are really chondromas which have undergone myxomatous or mucinoid degeneration. Local invasion occurs, but metastases are uncommon.

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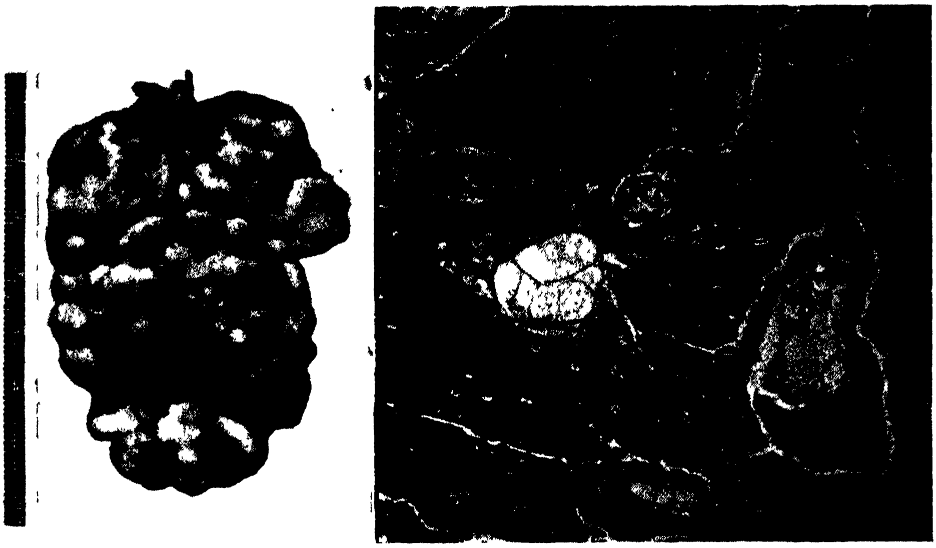
[1] " Thickened Ligamenta Flava in Low Back-Ache and Sciatica," by Carnegie Dickson and R. J. Twort, W.E.H., *Lancet*, 1940, ii, 1113. (*See* Fig. 791 opposite.)

Osteomas (p. 306) occur as exostoses or as enostoses. The **exostoses** are formed generally in fibrous tissue or in cartilage. They are frequently multiple, and may be symmetrical. They have been divided into the **ivory** exostoses when composed of dense, and **spongy** exostoses when of cancellous, bone. Some are formed from cartilage, and, in these, a layer of cartilage covers the ossifying tumour as long as it is growing. The spongy exostoses are found especially in connection with attachments of muscles—the ivory being common on the bones of the skull.[1] The **enostoses** are bony tumours which arise in the interior of the bone. Keith and others maintain that the multiple exostoses are due to a disorder of growth, and are not true tumours. Keith adopts the name, suggested by Morley Roberts for this condition—"**diaphysial aclasis.**"[2] In this disease, the normal "modelling-



(A) (B)

FIG. 792. *Ivory Enostosis* or *Osteoma Eburneum* of the skull: a tumour composed of compact bone growing from the inner aspect of the left frontal bone in a woman aged thirty-two. (A) Naked-eye photograph, two-thirds natural size. (B) Low-power view of section showing dense layers of compact bone containing comparatively few bone-corpuscles. A few small cancellous spaces containing fat-cells and thin-walled blood-vessels, but no blood-forming marrow-cells, are shown. (Removed by Mr. Wakeley, W.E.H.) Mallory's connective-tissue stain. × 100.

[1] For a note on "Hyperostosis Frontalis Interna," and its associated syndrome, *see* appendix at end of book, p. 1260.

[2] *a*- (alpha-privative), not: κλάσις, *klasis*, a breaking or fracture, whence, secondarily, a "modulating" (of the voice), and hence "modelling," the meaning here being—lack of modelling.

process " is arrested, and, between the properly-formed part of the shaft and epiphyseal end of the long bones, there is interposed an irregular cylinder of imperfectly modelled bone, on the surface of which there are, usually, several outgrowths. "**Diaphysial aclasis**" is, according to this view, primarily a disturbance of the growth-disks, and of both the cartilaginous and periosteal elements comprised within these disks. (*See also* p. 308.)

Myxomas, Lipomas and **Angiomas** occur, but are rare. **Hæmangiomas** may arise in the periosteum or in the bone-marrow. They have been found in the skull, the vertebral bodies, the bones of the limbs and the flat bones. The growth in the vertebral bodies may give rise to compression-myelitis of the spinal cord; and, in bones of the limbs, a cystic tumour may cause broadening of the shaft and spontaneous fracture.

Group II. Locally Invasive and Potentially Malignant Tumours. In this group we place the **giant-celled tumour—osteoclastoma** or so-called "**myeloid sarcoma**" ("**the epiphyseal giant-celled tumour**" of the classification given on p. 1225) and the **giant-celled epulis of the jaw.**

The **osteoclastoma** (p. 308) is regarded by many surgeons and pathologists as a "benign" tumour, but with this view we disagree. Our experience is that although in some cases of osteoclastoma secondary growths do not occur, and recurrence, after removal of the primary tumour, may not take place, **metastases are not uncommon** even after "removal" of the primary growth. This tumour is developed from the deeper layers of the periosteum or from the endosteum and *not* from the marrow-cells.[1] It occurs mainly in children and young adults and is found in bones developed from cartilage and especially at the lower end of the femur and upper end of the tibia. The tumour invades the tissues locally, and causes expansion and absorption of the bone so that the swelling in the limb gives a crackling sensation when handled, owing to the surface being covered with a very thin layer of bone. The tumour is soft and very vascular. Hæmorrhages into it are usual and the centre may consist of a semi-fluid mass, brownish in colour, from the presence of altered blood-pigment. Microscopically, the characteristic cells are the large, irregular and multinucleated giant-cells which resemble osteoclasts (Figs. 143–4, pp. 309–310). These are associated with both spindle-shaped, and less commonly small-round, cells similar to those of sarcomas. Spontaneous fracture of the bone may take place. Neither bone nor cartilage is formed by the tumour.

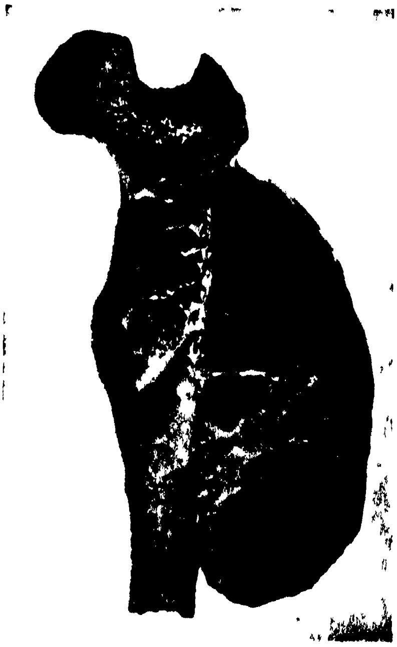


FIG. 793. *Osteoclastoma of Shaft of Femur.* Macerated and dried specimen showing expanded shell of bone.

By some, this lesion is regarded—without, in our opinion, any justification

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[1] It should, therefore, *not* be called a " myeloma " or a " myeloid sarcoma."

—as a chronic inflammatory affection and the large cells as foreign body giant-cells, but with this opinion we entirely disagree. The common view is that the growth is neoplastic and " benign " in character. The facts that, in some cases, metastases occur, and that these secondary growths show all the characteristic microscopical appearances of the original mass, certainly support the view that the growth is **neoplastic** and **potentially,** as well as, in a certain proportion of cases, **definitely, malignant.**

A giant-celled tumour of the jaw (**giant-celled epulis**) is not uncommon. It probably originates in the periosteum and may form a large pedunculated mass covered with mucous membrane which tends to become ulcerated. Microscopically, it is composed of interlacing spindle-cells with numerous giant-cells similar to those seen in the giant-celled tumours of long bones. It rarely recurs after removal and is generally considered to be a " benign " tumour, any " recurrence " being due to incomplete removal.

Ewing,[1] who supports the view as to the benign character of the osteoclastoma, states that " in a very few instances, usually after long periods of growth, and development the giant-celled tumour may prove fatal with pulmonary complications." Stating also that " there are many variations in the gross anatomy and structure " of these tumours, he described five variants, to which only brief reference need be made here.

(*a*) **Medullary spindle-celled** and **myxo-sarcomas**. These tumours may be firm and opaque, sometimes with a softened and reddish or hæmorrhagic centre and occasionally with a definite myxomatous structure. The giant-cells are scanty and often localised to certain parts of the tumour. The tumours proliferate actively and prognosis should be guarded. " Since there are many gradations between this and the typical giant-celled tumour, there is little doubt that the two forms are essentially the same process."

(*b*) **Xanthosarcomas** [2] are solid, firm, yellow growths, the colour being due to the presence of lipoid granules in large polyhedral cells. The growth may be extensive and rapid. the spindle-cells which are associated with the large polyhedral cells showing the most active growth. Giant-cells may be scanty. These tumours may recur after excision, but do not show any marked infiltrative growth.

(*c*) **Aneurysmal giant-celled tumours** [2] are composed of large blood-spaces filled with blood-clot and lined by giant-celled tissue. These tumours resemble very closely osteogenic sarcomas invading bone, opening into blood-channels and producing what might be described as aneurysmal dilatations, but they are said to be non-malignant.

(*d*) **Benign calcifying giant-celled tumours** are composed of round, spindle- and giant-cells with areas of calcification and of cartilage. The growth is slow, the mass may be shelled out and recurrence does not take place. It is suggested that the tumour originates in misplaced islets of cartilage.

[1] Ewing. " Neoplastic Diseases," 4th ed., 1940, p. 318.

[2] For the occurrence of so-called " xanthomatous " change and also the formation of blood-vessels and vascular spaces *as secondary phenomena in tumours, e.g.*, in meningiomas, *see* p. 1084 and Figs. 659 and 660, and also p. 1097. In our experience, these phenomena tend to supervene in *any* tumours which are liable to be the seat of hæmorrhage or of necrotic changes, and are comparable to similar changes in many inflammatory and degenerative lesions (Figs. 644–5, pp. 1055–6, and Fig. 749 (C), p. 1161). In this connection, *see* also note on the " Reticuloses and Reticulo-Endothelioses " and reference in it to " xanthomatosis, primary and secondary," in Appendix, p. 1263.

(*e*) **Malignant giant-celled tumours.** In one type of these, described by Ewing, the structure presented all the features of the typical giant-celled tumour, but the spindle-cells were very large and their nuclei hyperchromatic, and the giant-cells were of moderate dimensions with a reduced number of very hyperchromatic nuclei. Such tumours are malignant from their inception and give rise to metastases. Goforth, quoted by Ewing, states "that there are all grades of malignancy in giant-cell tumours, and that each must be estimated by its particular structure." Various authors have described malignant giant-celled tumours of bone.

Group III. Malignant Tumours. (*a*) **Osteogenic sarcomas (medullary, subperiosteal, periosteal: fibrosarcomas.** American classification). **Sarcomas** (p. 316) are the commonest form of malignant tumour of bone. They occur in almost any situation, but the sites of election are the metaphyses of the long bones and especially the femur, tibia and humerus. They may be **periosteal** or **endosteal** in origin. The former arise usually near the surface of the bone and at the end of the diaphysis, are highly malignant, penetrating the periosteum and invading the muscles. Tumours of the endosteal variety are less common, producing expansion and thinning of the compact bone ; and the tumour-cells may reach the periosteum and give rise there to an appearance similar to that of a primary periosteal sarcoma. Invasion of the bone-marrow usually occurs. The **primary periosteal sarcoma**, though tending to spread along the shaft and cause destruction of bone by invasion and erosion, with extension into the medullary cavity, is essentially a tumour derived probably from the outer layers of the periosteum, though tending to grow outwards without producing any marked changes in the shaft. Such tumours appear as fusiform swellings, grow rapidly, invade the soft tissues, and give rise to metastases. In those tumours of this type in which the shaft becomes involved, considerable resorption of bone and the formation of new spicules, *i.e.*, destructive and formative processes, often go on side by side. Spontaneous fracture is common, though the formation of new bone in the tumour may prevent its occurrence. The microscopical appearances vary considerably in the different types of growth. In the common type, the cells are mostly of the spindle-type (**spindle-celled sarcoma**) ; though, in rare instances, the tumours are composed largely of fibrous tissue with comparatively few cells, which show the hyperchromatic character of nuclei typical of malignant cells (**fibro-sarcoma**). In other instances, mixtures of round-cells, spindle-cells and giant-cells (**mixed-celled** and **giant-celled sarcomas**) are present (p. 319). This appearance usually suggests bone-marrow invasion, but the giant-cells may be foreign-body cells formed round blood-extravasations, and it is not uncommon to find in these tumours blood-vessels lined by tumour-cells.[1]

Local invasion is a constant feature and early occurrence of metastases is common, especially in the lung.

(*b*) **Telangiectatic osteogenic sarcomas.** In this type, the blood-vessels are numerous, thin-walled (sinus-like), and lined by tumour-cells. The tumour may be represented by an **aneurysmal sac** lined by spindle-shaped and polyhedral cells and giant-cells, and filled with blood-clot in which similar malignant cells are found. It occurs especially in children and young adults, is extremely malignant, causes rapid destruction of the shaft of the affected bone, and gives rise to spontaneous fracture and early metastases.

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[1] *See* second footnote on p. 1228.

(*c*) **Sclerosing sarcomas.** These resemble the medullary and subperiosteal type except that both the subperiosteal and the medullary portions are composed of dense, well-formed bony trabeculæ, with only a moderate amount of cellular tissue, spindle-celled in type. They usually progress slowly, the epiphyses may be involved, and the metastases which develop late in the disease in the lung tend to contain bone-spicules. Notwithstanding their dense consistence, the tumours are very vascular.

(*d*) **Angio-endotheliomas** and **diffuse endotheliomas.** The origin of these forms of malignant growths is not always clear, but some arise from the endothelium lining blood-vessels and lymphatic and others apparently from the reticular endothelium of lymphoid tissue—**angio-endotheliomas.** Ewing describes three cases at the lower end of the humerus which eroded the shaft, invaded the soft tissues and produced metastases in the lung. The cells were cuboid or cylindrical, and arranged in alveoli or cords, and the spaces contained circulating blood. They resembled the metastatic growths of renal carcinomas (so-called " hypernephromas ") or of true tumours of the suprarenal (p. 845 *et seq.*). Howard and Crile, quoted by Ewing, described multiple tumours of bone —**multiple endotheliomas**—in which the cells were large polyhedral plates with many giant-cells. Primary growths were found in the lumbar vertebræ, clavicle and ribs, with many metastases in liver, lungs, lymph-nodes, heart-muscle and skin. They believed that these originated from the endothelial cells of the lymph-spaces of the marrow.

Diffuse endotheliomas. Ewing has described a sarcoma occurring in young children, with symptoms resembling and liable to be mistaken for those of osteomyelitis—generally described as " **Ewing's tumour.**" The growth in one of his cases occurred in the os pubis of an infant of eighteen months. The tumour may appear in the small bones, in the flat bones, or at the end of the long bones, and has a tendency to affect a large portion of the shaft, causing absorption of the cancellous tissue and extending to the Haversian canals and the periosteum. The periosteum is soon perforated and the neighbouring soft tissues invaded. New bone is laid down in parallel lines or in irregular masses. The tumours are highly vascular, and hæmorrhage and necrosis in the central parts are common. The cells are polyhedral in shape and arranged in sheets, with a clear cytoplasm and small hyperchromatic nuclei. There is sometimes an imperfect alveolar arrangement of the cells, or a grouping round spaces in which blood may be circulating. Ewing states : " I have been unable to find any trace of osteogenic property in these tumour cells, nor has the origin of them been definitely established." His observations, however, suggest " that the process begins in the perivascular endothelium," but he states that " Connor concluded that the cells of the reticulo-endothelial system were the point of origin." It has, however, been pointed out that the reticulum-celled sarcoma, primary in lymph-nodes, and which invades bone, does not react in the same way as these diffuse endotheliomas. It also differs from osteogenic sarcomas and myelomas in various features. It originates usually as a single tumour, but, in some cases, the occurrence of multiple primary growths is suggested. It should, however, be remembered that, as the onset is slow, embolic distribution may account for the multiple character of the growths.

Myelomas (p. 319, and Figs. 153–4, p. 320). These malignant growths have their origin in the cells of the hæmopoietic bone-marrow and have been divided into groups according to the character of the cell from which they arise. The recognised types are (1) **Plasma-celled myeloma** ; (2) **Granular-celled myeloma or myelocytoma** ; (3) **Lymphocytoma** ; and (4) **Erythroblastoma.** These myelomas, or " **multiple myelomas** " as they are frequently called, arise usually as a single growth which may be of considerable size before multiple tumours appear. There is, however, evidence that, in some cases, the growths start at or about the same period in different situations. The commonest sites are the ribs and sternum, but tumours may arise in the vertebræ, skull, femur, pelvis and humerus (Fig. 153, p. 320). The naked-eye appearance varies in consistence and in colour. They may be soft or firm, and the colour depends on the vascularity. They may be pale- or deep-red. Necrosis and hæmorrhage are frequent accompaniments. There is marked absorption of bone, the growth may be contained in a very thin shell ; erosions, with multiple perforations or fractures, may occur and the periosteum and surrounding tissues become infiltrated. Though a fatal result may occur before metastases have developed, secondary deposits may be found in almost every organ in the body, but especially in the lung, lymph-nodes, liver, spleen, kidney and ovary. Anæmia may become severe, but there are no specific blood-changes. The urine is said frequently to contain an albumose which gives the " Bence-Jones reaction," *i.e.*, it is precipitated at 55° C., but more definitely at 65° C. ; and gradually re-dissolves at 85° C., to appear again on cooling. The exact nature and origin of this protein is not fully understood, nor is it invariably present. In many cases of myeloma, the disease is associated with some form of nephritis. The spleen is frequently moderately enlarged. Microscopically, the tumour-cells vary considerably in size and shape. They may be almost wholly of the plasma-celled type (**plasma-celled myeloma**) round or ovoid with non-granular cytoplasm and a relatively small excentric nucleus which is surrounded by a clear zone. In other cases, the cells are larger and contain neutrophil granules and are derived probably from the myelocytes or myeloblasts (**myelocytoma**). In this second group, polymorphonuclear leucocytes are often present. In the **erythroblastic type,** the cells may contain an excess of hæmoglobin, or the content may be reduced and the cells be small in size with a very dark-staining uniform nucleus. In the **lymphoblastoma,** there is a diffuse growth of small lymphocytes. These are very similar in appearance to the cells of lymphosarcoma.

In all types, the arrangement of the cells is diffuse and the stroma scanty. Though, in the early stages of the growth, the typical tumour-cells are intermingled with the normal cells of the bone-marrow, as the tumour progresses these typical marrow-cells gradually disappear. Little is known as to the ætiology of the disease, which occurs especially among males in middle life.

Chloroma (*see also* pp. 222, 319 and 636). This is a cellular tumour in which the cells may be of the lymphatic or of myelocytic character. Its conspicuous feature is the greenish or yellowish-green tinge which is attributed to the presence of lipoid granules in the cells. The tumours appear especially in the bones of the skull; but the sternum, vertebral column, ribs, pelvis, and occasionally the long bones, may be affected. The bone-marrow is regularly involved, but sometimes only in slight degree, though often very extensively. The metastases, often irregular in distribution, are a prominent feature and occur in almost every organ as well as in the skin, and in the muscles, particularly their tendinous insertions. Chloroma is practically always associated with a **leukæmic** state of the blood, and is now usually regarded as itself **a rare type of leukæmia** (p. 636).

Secondary sarcomas in bone, apart from those of melanotic type, are rare.

Metastases secondary to carcinomas of the breast, uterus, prostate, kidney, and lung are common. The bones most frequently affected are the ribs, vertebræ, sternum, skull and the upper ends of the femur and humerus. Occasionally, such secondary invasion of the bone-marrow is so extensive that almost no part of the osseous skeleton escapes, the term "diffuse carcinomatosis of bone" being applied to the condition (pp. 664 and 668).

Parasites :—

Hydatids of bone occur, but are rare. The hydatid-cyst or cysts may cause expansion of the bone. Certain protozoal parasites, *e.g.*, of malaria, are found in the bone-marrow and may be demonstrated by sternal puncture (p. 603 *et seq.*).

SECTION II

DISEASES OF JOINTS

MALFORMATIONS :—

Dislocations and Deformities of joints may be congenital or acquired. Among the more important of these are **congenital dislocation of the hip**—in which the head of the femur generally lies on the dorsum of the ilium above and behind the acetabulum, which is usually deficient—and the various forms of club-foot (talipes varus, valgus, equinus, and calcaneus, or combinations of these), knock-knee (genu valgum), bow-legs (genu varum), and flat-foot—for full descriptions of which reference should be made to surgical textbooks.

In some of the forms of talipes, the deformity is congenital in origin ; in others it is due to paralysis of certain muscles, the remaining (unparalysed) muscles pulling upon the foot and bringing about the deformity (pp. 1073 *et seq.*, 1172 *et seq.*, etc.).

INJURIES :—Lacerations of the synovial membrane, hæmorrhagic extravasations, suppuration, tearing of ligaments, displacements of cartilages, dislocations and fractures, are described in works on Surgery.

INFLAMMATORY, DEGENERATIVE, and PROLIFERATIVE CHANGES in JOINTS :—

(*a*) **SIMPLE, ACUTE or NON-SUPPURATIVE ARTHRITIS.**

(1) **Rheumatic Arthritis.** In this type, several joints may be affected at the same time or the condition may resolve in one joint, to be followed by an attack in another. The **synovial membrane** is congested, the congestion often being patchy in its distribution, infiltrated with inflammatory cells, mainly polymorphonuclear, and it, with the **articular cartilages,** may be covered with a thin fibrinous exudate. The joint-cavity contains clear or turbid, but rarely a purulent, fluid. Extension of the inflammation to the periarticular tissues and ligaments sometimes occurs, and localised foci of inflammation—**rheumatic nodules**—may be formed in the subcutaneous tissue, the periosteum or the intermuscular fibrous tissue. Endocarditis is a common complication and associated pericarditis or pleurisy may be present. The condition is frequently preceded by tonsillitis, and the channel of entrance for the infecting agent is then probably the fauces or the naso-pharnynx. In the majority of cases, the inflammation in the affected joints subsides and there is a return to normal, but relapses are common. The ætiology is still undetermined. Some authorities regard the reaction in the joints in this and in other non-suppurative joint-affections, such as those that occur in some cases of pneumonia, scarlet fever, and epidemic cerebrospinal meningitis, as allergic in nature and analogous to those which sometimes occur after injections of serum, but by many observers the streptococcus is regarded as a causal agent. One of us (J.M.B.) isolated from an area of congestion in the synovial membrane of a very acute case, dying with hyperpyrexia, a non-hæmolytic streptococcus of "fæcalis" type. This was obtained a few hours after death and, on intravenous injection into a series

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of rabbits, a "flitting" or transient arthritis with resolution and subsequent relapses and in some instances a well-marked endocarditis were produced. The blood of the patient, from whose knee the organism was obtained, gave no growth of bacteria on prolonged cultivation, and streptococci were not found in the blood of the infected rabbits.

(2) **Gonorrhœal Arthritis.** In the acute cases, the inflammatory reaction resembles that seen in acute articular rheumatism. There is swelling of the joint, with a moderate amount of turbid, but not frankly-purulent, fluid and no destruction of tissue. The disease is usually a polyarthritis, though one joint only, especially the knee, may be involved. Complete resolution may take place. The commoner form is a chronic infection in which there is involvement of the surrounding tissues—ligaments, tendons, etc., with the formation of fibrous adhesions and persistent stiffness or even fixation of the joint. In the acute form, with effusion into the joint, the gonococcus may be found in the leucocytes of the fluid, though often only after considerable search (pp. 902–3 and 905).

(3) **Gouty Arthritis.** In this disease, the urate of sodium is deposited in the form of acicular crystals, in the first place in the cartilages, especially towards the surface; and, later, in the synovial membranes, ligaments, bones, and soft tissues round the affected joints (Figs. 106–7, pp. 216–17). Some authors regard a primary degeneration of the cartilage and cartilage-cells as an essential preliminary to the deposit of the urates within them. The crystals cause considerable irritation, and produce an acute, sub-acute, or chronic inflammatory reaction. Suppuration never occurs in uncomplicated gout. The joints most frequently involved are the small articulations of the hands and feet (pp. 215–18).

(*b*) **SUPPURATIVE ARTHRITIS.** This may result from a secondary infection of a non-suppurative arthritis with pyogenic bacteria; or it may be purulent from the first. Bacteria may be introduced through an open or perforating wound, or the joints become involved by spread from a neighbouring osteomyelitis, epiphysitis, bursitis or cellulitis. In pyæmia, an acute infection of the joints, with rapid suppuration, may develop, the whole joint-cavity becoming distended with pus. Similarly, in scarlet fever, typhoid and paratyphoid fevers, pneumonia and epidemic cerebrospinal meningitis, a purulent arthritis is sometimes found, though in these diseases a non-suppurative form may occur. In the purulent type, the synovial membrane becomes thickened, infiltrated with inflammatory cells and converted into suppurating granulation-tissue. The inflammation spreads to the articular cartilages, which become softened and eroded: to the ligaments, which become completely disorganised: and to the periarticular tissues, into which the pus may burrow. Eventually, these cartilages undergo necrosis and absorption, the ends of the bones show rarefying osteitis, the periosteum is inflamed and, later, new bone with osteophytic projections may develop. Even at an advanced stage, however, the inflammation may subside; but usually some degree of rigidity or even complete ankylosis—fibrous or osseous—remains.

(*c*) **CHRONIC RHEUMATIC and RHEUMATOID ARTHRITIS.** The changes in the joints in these two conditions resemble one another in some features. Until more information is obtained as to the causal agent or agents, the classification of these chronic joint-affections must remain in an unsatisfactory position. In a proportion of cases of rheumatoid arthritis, the clinical history indicates the repeated occurrence of infections in the mouth, nose and paranasal sinuses, intestine, prostate, cervix uteri or other situation, and definite foci of infection in the teeth, tonsils or elsewhere are frequently present. The cure or removal of these foci of infection is often followed by improvement in, or arrest of, the rheumatic lesions. Various bacteria, especially streptococci and staphylococci, have been isolated from the synovial membranes of the affected joints, and, as a result of the inoculation of the organisms so obtained into rabbits, either intravenously or directly into the joints, a chronic arthritis with proliferative overgrowth and ulceration of cartilage has been produced. The evidence at present available suggests that rheumatoid arthritis is a chronic infective disease of the synovial membranes and periarticular tissues, secondary to some primary and probably slowly-developing streptococcal lesion elsewhere in the body ; but typical rheumatoid arthritis has not been produced experimentally, and, though subcutaneous nodules similar to those which are characteristic of acute rheumatic fever are found in from 10 to 20 per cent. of the patients suffering from the disease, there is as yet little clinical evidence that chronic rheumatoid arthritis is directly related to acute rheumatism.

The subcutaneous **rheumatic nodules** are characterised by a central area of necrosis, surrounded by a zone of large mononuclear cells. The arterioles in the neighbourhood show endarteritis obliterans.

(i) **Chronic Rheumatic Arthritis,** *i.e.*, the chronic form of arthritis which is a sequel of acute rheumatism, is characterised mainly by pain and stiffness in the joints ; but these symptoms are due to chronic inflammatory changes in the ligaments, synovial membranes, periosteum, the fibrous tissue of muscles, the subcutaneous fibrous tissue and sheaths of nerves. At first, an acute inflammatory œdema, causing swelling of the connective-tissue fibres, is a pronounced feature. Later, proliferation of the connective-tissue cells, with increased fibrosis and sclerosis of the tissues surrounding the affected joint, takes place. Stockman of Glasgow (1920) described this condition of **fibrositis** (p. 1249) in relation to so-called " muscular rheumatism." He regarded it as a sequel to acute rheumatism, gonorrhœal infection or influenza, and stated that it was common in rheumatoid arthritis. This association of chronic rheumatism with rheumatoid arthritis may account for the view of those authors who regard them as identical diseases having a common cause and essentially similar pathological results.

(ii) **Rheumatoid Arthritis** occurs especially in women, and affects first the smaller joints of the hands and feet—the interphalangeal joints of the fingers being as a rule the earliest to be attacked. The wrists, knees, and ankles may be affected comparatively early ; and, later, the vertebral and temporo-maxillary joints may become involved. The hip-joint usually escapes. In the early stages, the changes appear particularly in the synovial membranes, which show an increased vascularity, and become thickened and infiltrated with vascular granulation-tissue. There is, usually, excess of synovial fluid. The synovial fringes enlarge, and papilliform projections are formed at the margins of the joints. These are produced by a proliferation of connective tissue, are covered by serous membrane, and, in them, cartilaginous nodules may form. Fat is sometimes deposited in the fringes. Some of these projecting masses occasionally become detached and form "**loose-bodies**" in the joint-cavity (p. 1241).

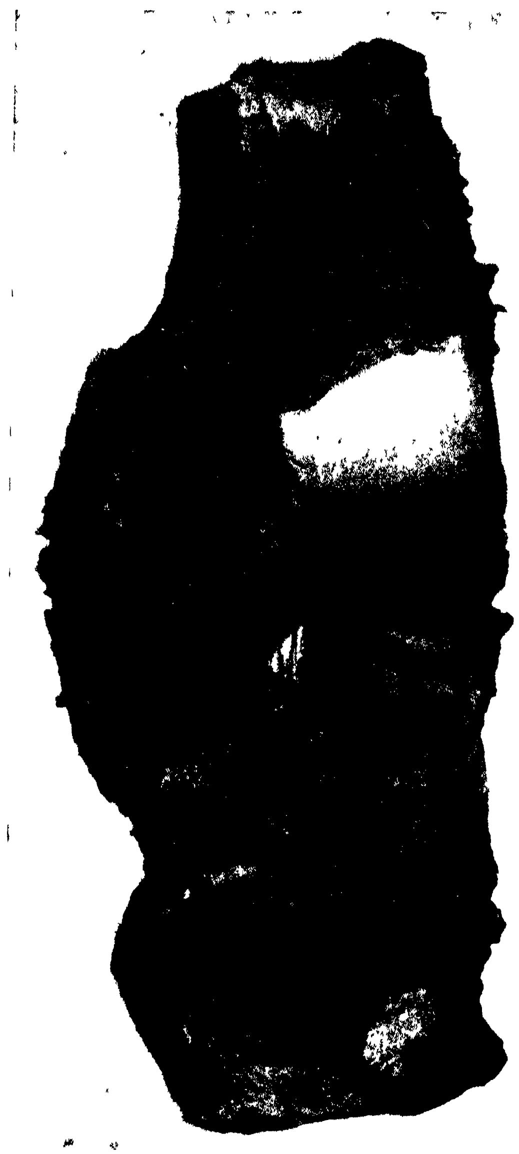

FIG. 794. *Chronic Rheumatoid Arthritis:* showing proliferated synovial fringes and projecting papilliform bodies: "lipping" of the articular margins: and invasion of the cartilage over the inner condyle of the femur by the proliferated synovial fringes.

Calcification or ossification is liable to take place in these fringes, though such changes are commoner in osteo-arthritis.

The articular cartilages become softened—especially where the surfaces are in contact with one another—and assume a fibrillated or velvety appearance. At a later stage, erosion and destruction by granulation-tissue takes place, the cartilages being at parts rubbed away by friction; at the same time, proliferation of the cartilage may cause it to extend beyond its normal limits; and, if this overlapping cartilage becomes calcified or ossified, considerable deformity and lipping of the articular surfaces of the bones is produced. The cartilage becomes somewhat translucent. Though the articular ends of the bones in many cases for a considerable period show little pathological alteration, extensive softening of the bones, with rarefaction and increased porosity, and, in some cases, enlargement, may be present. The surface, where deprived of its cartilage, may become smooth and polished like ivory—eburnation (Fig. 795). Associated with these changes there is often considerable thickening of the ligaments and other fibrous structures round the joints, great muscular wasting, especially of the extensors of the fingers, and impairment of the movements of the joints. Ankylosis, generally fibrous, but sometimes bony, may follow. The spleen and lymph-nodes are often enlarged, especially in children.

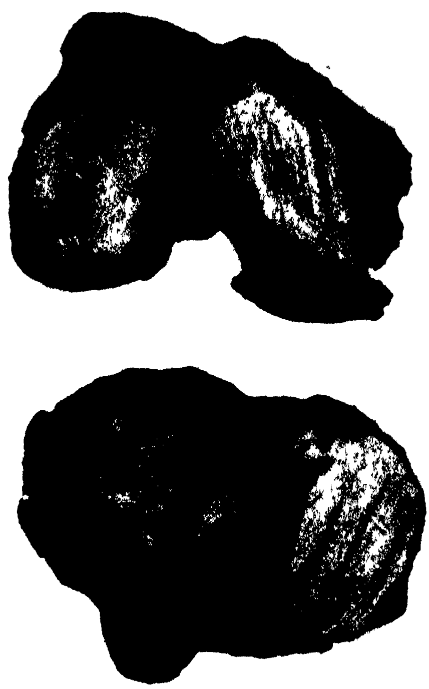

Fig. 795. *Chronic Rheumatoid Arthritis.* The articular ends of the tibia and femur, showing eburnation of the surface of the internal tuberosity and the internal condyle, with antero-posterior grooving. The articular surfaces also show lipping.

(*d*) **STILL'S DISEASE.** In this form of **chronic infective arthritis affecting children,** first described by Still in 1897, there is stiffness and fusiform swelling of the joints, due mainly to synovial and periarticular thickening. The cartilages may become pitted and eroded, but the bones usually are not affected, and ankylosis does not occur. The disease, which may closely resemble the rheumatoid arthritis of adults, commences commonly before the age of the second dentition, and is characterised especially by hard, painless enlargement of the lymph-nodes, and, frequently, by splenic hyperplasia and some degree of anæmia. Muscular atrophy round the affected joints—knees, ankles, wrists and neck—is a pronounced feature. Numerous joints may become involved successively. The disease is commoner in girls than in boys, commences between the ages of two and five years with an acute illness characterised by multiple arthritis, fever, leucocytosis and enlargement of spleen and lymph-nodes. Recovery may take place, but the usual result is more or less severe crippling. Colver [1] (1937) followed up the history of 49 cases from the Children's Hospital, Great Ormond Street, London. Of these, 19 were free of joint-pain and tenderness for a period of not less than two years, 12 were dead, and 18 showed active disease. Of the 19 quiescent cases, 7 recovered completely, 8 were crippled, and 4 had only occasional joint-pains.

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[1] "Prognosis in Rheumatoid Arthritis in Childhood," by Thomas Colver, *Archives of Disease in Childhood,* 1937, **12,** 353.

(*e*) **OSTEO-ARTHRITIS** or **ARTHRITIS DEFORMANS.** This condition is commoner in men than in women and is a degenerative disease of the later periods of life. The large joints are those usually involved and sometimes only one joint—the hip-joint particularly—but the small joints of the hands and feet are occasionally attacked. Small bony outgrowths at the sides of the phalangeal joints (Heberden's nodes) are sometimes seen and have been associated with a mild form of osteo-arthritis. The articular cartilage becomes softened and lustreless, and its matrix fibrillated. Erosion of the cartilages takes place, the underlying bone often shows parallel grooving ; and this erosion, combined with an associated proliferation at the edges of the cartilages, gives rise eventually to the formation of osteophytes. In the hip-joint, the head of the femur becomes enlarged, and proliferative outgrowth at the articular margins may be considerable, producing an irregular ring or everted lip of bone encircling the head. A similar projection of bone takes place at the margin of the acetabulum ; and, in this way, great impairment of movement results. The head of the bone becomes worn away, sometimes to an extreme degree, and the surface becomes polished and enamel-like at the areas of contact (**eburnation**). The compact bone may become thickened and sclerosed, but in some cases the cancellous bone becomes attenuated and absorbed and the head of the femur becomes flattened and the neck shortened. Bony ankylosis does not occur. The synovial membrane shows villous overgrowth and considerable fatty invasion, and the villous outgrowths may become detached and form " **loose-bodies** " in the joint-cavity (p. 1241). The ligaments and the trans-articular tendons are liable to undergo degeneration and disappear. In this condition, there is no exudation into the joint-cavity. As to the ætiology of this disease, nothing is known. There is no direct evidence of bacterial infection or of any characteristic lesion in the nervous system. It is a slowly-developing senile change, often associated with arteriosclerosis. Its occurrence in the hip-joint suggests that trauma may play a part. Unlike rheumatoid arthritis, which commences as a chronic infection of the synovial membrane, this disease is a degenerative process and the causal factor affects the nutrition of both cartilage and bone simultaneously.

(*f*) **SPONDYLITIS DEFORMANS.** This disease is characterised by extreme rigidity of the spine, which may be straight and poker-like or may show kyphosis. The kyphosis may affect the whole spine or sometimes is present only in the cervical and thoracic regions. Great deformity results. Radiography shows that minor degrees of the disease are not uncommon in elderly people and especially in males. The cause is unknown, but it is claimed that the reactions leading to rigidity are a sequel to degenerative changes in the intervertebral disks, perhaps following some infective or metabolic diseases, and that the irritation causing the overgrowth is of an inflammatory or toxic nature. The ossification of the ligaments and bony ankylosis, which are the main pathological features in this disease, seem to separate it definitely from osteo-arthritis ; and the pronounced changes which take place in the ligaments suggest that a chronic inflammation of the fibrous tissue, with bone-formation in it, is a more likely cause of this disease than a degeneration of bone and cartilage such as occurs in osteo-arthritis. The most obvious pathological results of the disease are the bony outgrowths at the margins of the vertebræ ("lipping") and bony ankylosis between adjacent vertebræ. The intervertebral disks may show an irregular fibrillated structure and may atrophy or become ossified and the spinal ligaments may also ossify. Similar ossification is sometimes present in the ligaments of the costo-vertebral articulations and occasionally in the large joints of the extremities. The pain associated with this disease has been attributed to compression of the nerves due to the narrowing of the intervertebral foramina, but at autopsy the foramina usually have been found quite patent (*compare and contrast* Fig. 790, p. 1223). The disease is not confined to the human subject, but occurs also in horses, cattle and other animals.

(*g*) **NEUROPATHIC ARTHROPATHY.** This term is applied to certain degenerative, destructive and proliferative changes which occur in joints in association with various nervous diseases, *e.g.*, tabes dorsalis, syringomyelia, and, according to Worster-Drought (1937), sometimes in the "progressive muscular atrophy" and "amyotrophic lateral sclerosis" forms of motor-neurone disease (p. 1171); and which are regarded as due in large part to neurotrophic disturbances. The joints affected have some relationship to the particular region of the spinal cord in which the degenerative lesions in the nerve-cells and tracts or fibres are situated. Thus, in tabes dorsalis, the joints of the lower extremities, and particularly the knee-joints, are affected in a large proportion of the cases; whereas in syringomyelia (p. 1163), which is found usually in the cervical region of the cord, the joints of the upper extremities are involved (Fig. 798). The pathological changes in these joints are essentially similar to those seen in the various forms of chronic arthritis—viz., destruction of cartilage, and proliferative overgrowth of the synovial membrane and of the articular ends of the bones, and, in some cases, atrophic changes. The most typical example is that known as **Charcot's joint** or **tabetic arthropathy,** which occurs in about 4 per cent. of cases of tabes dorsalis. In this affection, a painless effusion takes place into the joint, most frequently

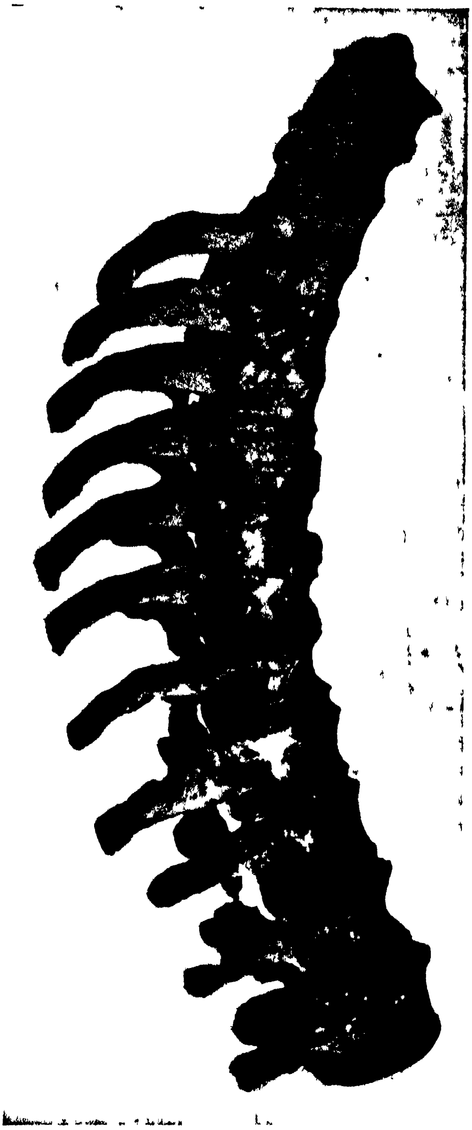
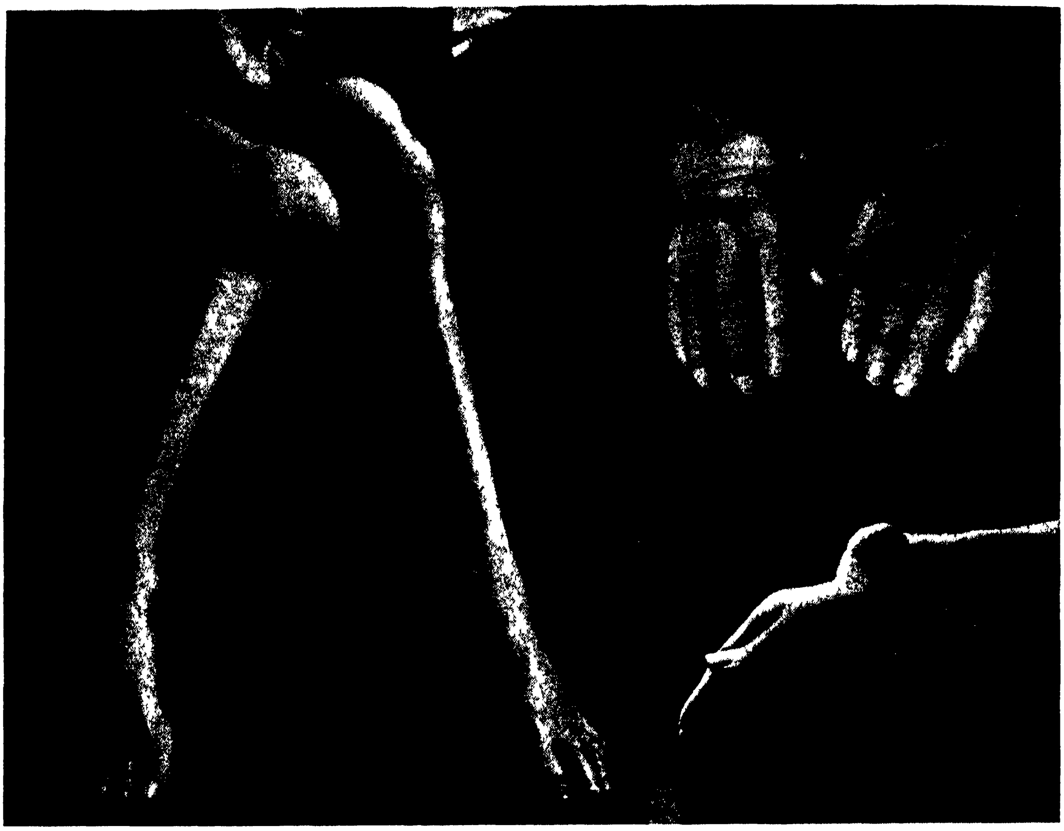


Fig. 796

ankylosis. Note the nodular masses of new bone, bridging across the intervertebral disks, and costo-vertebral joints.



(A) (B)

Fig. 797. *Tabetic Arthropathy* (*Charcot's Joints*).

(A) *Tabetic arthropathy of the right knee-joint* in a female aged sixty-five, with twelve years' history of ataxia, the joint-condition having been present for two years. Wassermann reaction weakly positive in both blood and cerebrospinal fluid.

(B) *Tabetic arthropathy of the wrist-joints* in a man, a house-painter, aged fifty. Joints affected painlessly for ten years. Wassermann reaction positive and colloidal-gold curve " luetic " in type.

(By courtesy of Dr. Worster-Drought and Dr. T. Rowland Hill, W.E.H.)

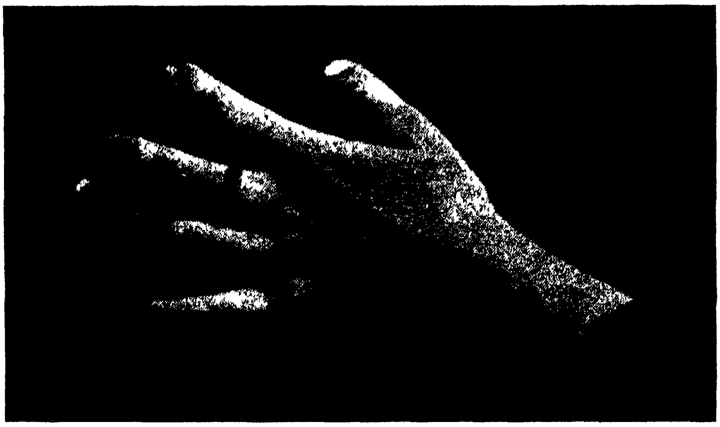


Fig. 798. ***Syringomyelic Arthropathy*** **(Morvan's type) of left hand of a female patient aged 23 years, showing the characteristic stumpy, truncated fingers—the terminal phalanges of the thumb and index-finger having disappeared—combined with some degree of subcutaneous œdema (the " main succulente " of Marinesco). (*See* p. 1165). (By courtesy of Dr. Reynell and Dr. Worster-Drought, W.E.H.)**

the knee-joint, leading to great distension of the capsule. Sometimes the effusion extends into the surrounding tissues, producing a solid œdema. The articular cartilages become eroded and absorbed, the synovial membrane may show villous projections which later become calcified to form osteophytes, and the articular ends of the bones show great irregularity. Usually there is atrophy of the bone ; but in rare cases hyperplastic changes occur. The destructive process may be so extensive that the whole joint becomes disorganised and flail-like, with varying degrees of displacement and even dislocation (Fig. 797).

Osteochondritis deformans juvenilis coxæ [1] (" Legg-Calvé-Perthes disease " —*see* p. 1204). This epiphyseal affection, now regarded as definitely *non*-tuberculous, occurs in children, especially boys, between five and ten years of age, and is characterised by erosion, flattening and lateral expansion of the epiphysis, and concurrent thickening and shortening of the neck of the femur —usually, but not always, unilateral, and liable to be followed by osteo-arthritis. This form of osteochondritis of the hip-joint was formerly believed to be a mild tuberculous affection, but some writers now regard it as a low-grade infection, perhaps staphylococcal, associated with or supervening upon interference with the blood-supply of the epiphysis and usually following on trauma. A somewhat analogous condition may attack the vertebræ and simulate Pott's disease. Osteochondritis of the hip was formerly believed to be a mild tuberculous affection, but the present view is that it results from interference with the blood-supply of the epiphysis following trauma. Some writers regard it as a low-grade infection—a chronic osteomyelitis.

LOOSE-BODIES in JOINTS. These may occur in otherwise apparently healthy joints, in which they are usually the result of trauma—portions of cartilage, or cartilage and bone, becoming detached and lying free in the joint-cavity, or remaining partially adherent at their site of origin. These bodies may, in the knee-joint, become arrested between the anterior surface of the bones and the capsular ligament and produce sudden " locking " of the joint. They are a cause of recurrent attacks of synovitis.

Loose-bodies are formed also in previously diseased joints, and are composed of detached fragments of cartilage, hypertrophied synovial fringes, bone, or, perhaps most commonly, either wholly or in part, of fibrinous exudate. The first three varieties are seen especially in cases of rheumatoid arthritis (p. 1236) and arthritis deformans (p. 1238) ; whilst the last-mentioned are of common occurrence in arthritis with exudation (*e.g.*, tuberculous arthritis—p. 66), and constitute the so-called " melon-seed " or " rice-bodies."

Joint-Disease in Hæmophilia. Effusion of blood may take place into the knee, or, less commonly, into other joints, in cases of hæmophilia (pp. 670–1). The blood may be absorbed completely, or the bleeding may recur. In some cases, adhesions are left ; and, in others, changes like those seen in osteo-arthritis develop.

Tuberculous Disease and Syphilis of Joints (*see* Granulomata, Chapter III, pp. 66 : and 83 and 85).

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[1] For this and allied conditions, *see* : J. Buchman, " A Résumé of the Osteochondritides," *Surg., Gynecol. and Obstet.*, 1929, **49**, 447 : also H. Platt, *Brit. Jour. Surgery*, 1922, **9**, 366—in both of which references are given and the radiological findings illustrated.

SECTION III

DISEASES OF THE VOLUNTARY MUSCLES AND TENDONS

Muscle-fibres are enclosed in a delicate sarcolemma-sheath, and are bound together by interstitial connective tissue in which many of the pathological changes affecting muscle take their origin—the muscle-fibres undergoing secondary degeneration or absorption.

The changes which occur in muscle during the production and passing off of **rigor mortis** are described on p. 234, and the processes of **healing** and **regeneration** on p. 53.

RUPTURE of muscles—apart from injury—may arise from sudden or violent contraction, and may involve only a few fibres or numerous strands of the muscle. The condition is usually accompanied by a considerable amount of hæmorrhage and swelling. A reference to rupture of tendons will be found on p. 1252.

Myohæmoglobinuria (p. 862). After severe and extensive *injuries to muscle*, the myohæmoglobin freed from the muscle-substance may be excreted by the kidneys and be found in the urine.

HÆMORRHAGES into and between the muscle-fibres are common in fevers, *e.g.*, in cerebrospinal fever and typhoid fever, in hæmorrhagic diseases such as scurvy, purpura hæmorrhagica and hæmophilia, in septicæmia, and in cases where there is an excessive action of the muscles, *e.g.*, in tetanus and other convulsive disorders. Usually, the hæmorrhagic areas are minute ; but, in scurvy and in hæmophilia, large extravasations may be found, which tear and push aside the muscle-fibres.

ŒDEMA. The intermuscular connective tissue, and the muscles themselves, may show considerable œdema in nephritis, anæmia, and other conditions which give rise to local or general œdema (p. 179 *et seq.*).

DEGENERATIONS. Cloudy swelling and fatty degeneration are common as a result of toxic infection in general infective diseases ; and fatty degeneration follows disuse from paralysis and occurs also in so-called " blood-diseases," phosphorus-poisoning and other allied conditions ((pp. 196–7). Calcification is found occasionally as a sequel of other degenerative changes in the muscle itself ; but it originates more commonly in the intermuscular tissue, secondary to non-suppurative or suppurative inflammatory conditions. It may occur also in and around parasitic cysts, *e.g.*, those of *Trichinella spiralis* (pp. 239 and 417–19).

NECROSIS of muscle-fibres occurs in fevers and other toxic diseases, and also may result from their invasion or compression by malignant growths. The muscle-fibres become more homogeneous in appearance and are somewhat swollen, their nuclei having lost the power of taking up basic stains.

Coagulation-Necrosis (Zenker's Degeneration) (p. 13 : pp. 248–9 : and Fig. 117, p. 249) occurs especially in typhoid fever and similar diseases. The muscle-fibres are swollen, present a homogeneous appearance, have lost their striation, and finally break up into small translucent masses which gradually become absorbed. Hæmorrhages into the degenerated areas are not uncommon. The abdominal muscles, the psoas, and the adductors of the thigh are its usual sites.

Though found especially in typhoid fever, a similar coagulation-necrosis may occur in any severe fevers such as smallpox or scarlet fever, as well as in a variety of other conditions.

ATROPHY. In atrophy of muscle, the striation becomes poorly marked or is lost, the fibres show vacuolation, fragmentation, granularity, or may appear hyaline in character. The sarcolemma-nuclei are increased in number and there is a relative increase in the interstitial fibrous tissue. Fatty tissue may be entirely absent or may be increased considerably in amount (pp. 195 and 262–3) and even entirely replace the paralysed and degenerated muscle (Fig. 754, p. 1173).

The causes of muscle-atrophy are dealt with under Atrophy, p. 257 : and also on pp. 1169 and 1180 *et passim.*

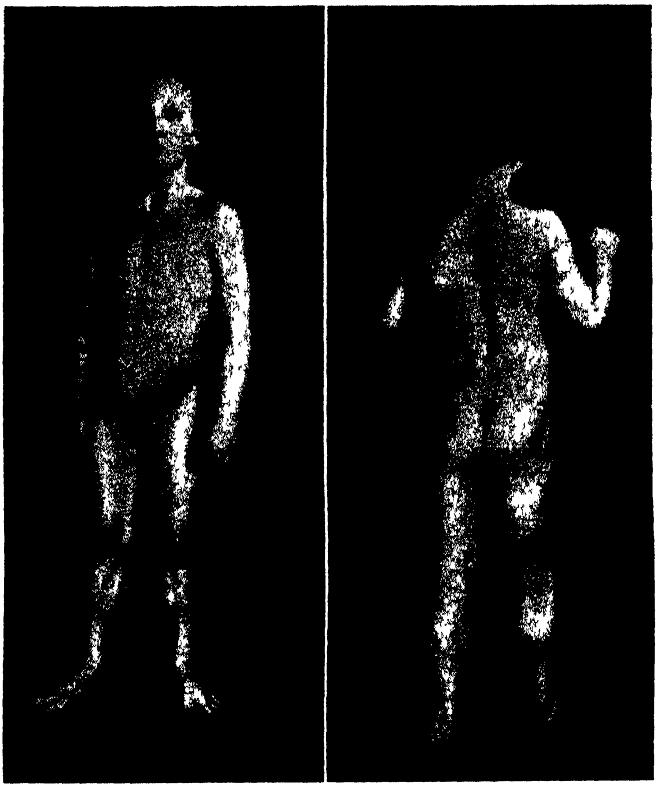

FIG. 799. *Pseudo-hypertrophic Muscular Dystrophy :* the so-called " Infant-Hercules " appearance in a boy aged eight years. (By courtesy of Dr. Reynell, W.E.H.)

THE MUSCULAR DYSTROPHIES. (the **Myopathies**). In this group of disorders of muscle, the two main forms are **pseudo-hypertrophic dystrophy** and **myopathia hypertrophica vera.** The former is the commoner and seldom develops after puberty, the latter is rare, but in their basic pathology there is no sharp division between them. Both begin in childhood or even in intra-uterine life and possibly are related to some congenital defect in the muscles. Several members of a family may be affected, and, though both sexes may be attacked, it is commoner in boys, and is transmitted only by apparently healthy females. Its ætiology is unknown, and there is no proof supporting the views that disease of the motor neurones, the sympathetic system or the pituitary gland is present as a causal factor.

Erb maintained that, in all cases, there is, first, hypertrophy of the muscle-fibres, and a slight increase in the amount of connective tissue. Later, atrophy supervenes—the muscle-fibres become vacuolated and fragmented, the sarcolemma-nuclei greatly increased in numbers, and the connective tissue in and between the bundles increased in amount. Fat is deposited in varying degree in this new connective tissue—sometimes so abundantly as to produce large masses of fatty tissue (Fig. 95, p. 195), which clinically give to the affected part the appearance of hypertrophy (Fig. 799, p. 1243). Whether this view of Erb is correct or not, the histological findings give evidence of the presence of both enlarged and degenerated or atrophied fibres in the affected area. Some of the "hypertrophied" fibres show well-marked striation, whilst others have become homogeneous, granular or vacuolated.

In different instances, special groups of muscles are affected. Thus, in some of the cases occurring in infancy, the muscles of the face show the involvement early in the disease; whilst in others the facial muscles escape and the muscles of the shoulder-girdle especially are affected. Other varieties of the disorder, differing in the situations of the affected muscles, the age at which the disease develops and the familial characteristics, have been described by Karnes and various other authors.

The changes are most characteristic in the **pseudo-hypertrophic** forms, particularly in the muscles of the calves, the extensor muscles of the leg, the glutei, lumbar muscles (Fig. 95, p. 195), deltoid, and triceps. Except in the special instances already mentioned, the muscles of the neck, face, and forearm and hands are rarely involved. The fibres of the heart-muscle may show the same changes in minor degree.

Einarson (1933–37) and Ringsted[1] (1938) of Aarhus and Copenhagen, suggest, as the result of experiments on rats, that the muscular dystrophies are deficiency-diseases due to a chronic absence from the diet of vitamin E. They found degenerative lesions in the cells of the ventral horns in the lumbar region of the cord, and degeneration and atrophy of peripheral nerves and of the muscles supplied by these; and they state that the lesions on the whole give the anatomical picture of spinal progressive muscular atrophy—ataxia of the hind-limbs, flaccid paralysis and gross wasting of the muscles—(see under "Motor-neurone Disease," p. 1169 *et seq.*). Working on this hypothesis, Bicknell[2] (1940) treated for prolonged periods cases of muscular dystrophies with freshly made dried whole-meal germ in half-ounce doses twice daily (wheat-germ oil or its active principal α-tocopherol has similarly been used for this purpose), and claims that, in the majority of the early cases, recovery took place. He concludes that the muscular dystrophies are deficiency-diseases, due, at all events in part, to the absence or an insufficient supply of vitamin E (pp. 441–2).

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[1] Larus Einarson and Axel Ringsted: "Effect of Chronic Vitamin E Deficiency on the Nervous System and the Skeletal Musculature in Adult Rats: A Neurotropic Factor in Wheat Germ Oil." Copenhagen and London, 1938.

[2] Franklin Bicknell, London, "Vitamin E in Muscular and Nervous Diseases," *Lancet*, 1940, i, 10.

MYASTHENIA GRAVIS. In this disease there is abnormal muscular weakness, and ultimately paralysis of certain groups of muscles, especially those of the eyeball and the face and the muscles innervated from the medulla, *i.e.*, a form of bulbar paralysis.

Microscopically, the affected muscles are found to be infiltrated with collections of small round (lymphocyte-like) cells, but no obvious degenerative changes are present. These groups of cells are found also in the myocardium, in the liver, suprarenals and other organs. In about half of the recorded cases, a hyperplastic enlargement of the thymus has been noted, and in some of these it has been stated that improvement has followed upon its artificial atrophy by irradiation or its surgical removal. Though no conclusive evidence as to the ultimate cause of the disorder has been brought forward, it has been proved that a chemical defect in innervation at the neuromuscular junctions—a deficiency in the formation of acetylcholine —is an essential factor in the production of the disease. Observing that the character of the functional abnormalities of the muscles in myasthenia gravis was similar to those occurring in **curare-poisoning,** and knowing the antagonism between **physostigmine** and **curare,** Dr. Mary Walker (1934) treated some cases of myasthenia with physostigmine and found that the muscle-weakness and fatigue were temporarily abolished. Later (1935), she reported that more satisfactory results were obtained if **prostigmin**—a synthetic analogue of physostigmine—is substituted for physostigmine. There was, with prostigmin, an absence of the toxic effects liable to follow the physostigmine-treatment. Previous and later observations by various authors [1] have helped considerably in the explanation of these results. A substance, **acetylcholine,** is produced at certain neuro-muscular junctions on the arrival of a nerve-impulse, and this substance transmits chemically the effects of the nerve-impulse from the nerve-endings to many of the specialised cells in the organs and tissues throughout the body, producing in those cells a physiological reaction either of stimulation or inhibition. The method of production and the origin of the acetylcholine are still unknown, but this substance is rapidly hydrolysed by a **choline-esterase** which is present in considerable amount in the sympathetic ganglia. This hydrolysis is inhibited by physostigmine. Experience has shown that the subcutaneous injection of physostigmine in man brings about a depression of the esterase activity, and therefore an intensification and prolongation of the action of acetylcholine. The synthetic substance, prostigmin, as mentioned above, produces the same reaction in a more intense degree. Lanari [1] (1936) observed that, when he gave 0·04 gramme of acetylcholine by intra-arterial injection, there was no apparent effect on the muscles in **normal** subjects: moderate contractions in patients suffering from **pyramidal lesions** associated with flaccidity: slight twitches only in the case of those with **extra-pyramidal lesions** and in **myopathies**: and muscular contractions in cases of **myotonia.** The specific effect of prostigmin in myasthenia gravis, to which reference has been made above, and the reaction between that drug and acetylcholine suggest, according to Fraser,[1] two possible explanations of the pathology of the disease. "(1) There may be a disturbance of the normal balance between acetylcholine production and its destruction by choline esterase—either a defective production of acetylcholine or an abnormally rapid destruction of acetylcholine by esterase, so that a deficiency of the transmitter of the effect of the nervous impulse results and prostigmin by inhibiting the esterase restores the balance ; or (2) there may be a curare-like substance present in myasthenia gravis that interferes with the transmission by acetylcholine to the muscle and is antagonised by prostigmin, which potentiates (gives power to) the transmitter." (*See* footnote below—*B.M.J.*, p. 1351.)

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[1] "Treatment of Myasthenia Gravis with Physostigmine," by Mary B. Walker, London, *Lancet*, 1934, i, 1200, and "Treatment of Myasthenia Gravis with Prostigmin," by the same author, *Proc. Roy. Soc. of Med.*, 1934–5, **28**, 759. "Prostigmin in Myasthenia Gravis," by

There is no evidence that the esterase-content of the serum is increased, and some estimates indicate that it is lower in the serum of cases of myasthenia gravis than in normal subjects ; but it has been suggested that the activity of the esterase at the neuro-muscular junctions may be increased even with a normal serum esterase-content. This, however, is difficult to prove.

To test the theory of the defective production of acetylcholine, Fraser and his co-workers injected choline-esters into two cases of myasthenia gravis, and found that improvement in muscle-power followed subcutaneous injection of 500 and 600 mgr. of acetylcholine, and smaller quantities of allied substances, **carbaminoyl-choline-chloride** ("**doryl**") and **acetyl-β-methyl-choline-chloride** ("**mecholin**" or "**mecholyl**"). The improvement was most pronounced with doryl, and the effects differed from those produced by the injection of prostigmin in that they appeared later, attained their maximum after some hours, and did not pass off for more than twelve hours. These workers considered that their results suggested some defect in the production of acetylcholine in myasthenia gravis. There seems, however, to be more satisfactory evidence in favour of the second hypothesis. Pritchard[1] (1935) found that the electro-myogram in myasthenia gravis is abnormal in that it shows a quick fatigue with high rates of stimulation, and that prostigmin not only produces improvement in the condition but restores the myogram to its normal form.

Taking into consideration all the experimental and other evidence, it can be said that, at present, there is no satisfactory explanation for all the facts ; but the occurrence of a curare-like poisoning of the muscles is more consistent with these facts than is a defect in the production of acetylcholine.

It may be that the beneficial effect of prostigmin and similar substances is due to their own action, or indirectly to that of some resultant product which overcomes the curare-like action on the muscle of some abnormal, and as yet undiscovered, chemical substance present in myasthenia gravis.

An endocrine basis has also been suggested, but without as yet conclusive evidence, though, as mentioned on pp. 839 and 1245, improvement in the muscular weakness and general health has been stated to follow diminution in activity or complete excision of a hypertrophic thymus. In this disease, as well as in other diseases of muscle, an abnormal metabolism of creatin and creatinine is frequently present. There is no true muscular atrophy, and no definite pathological lesion has been found in the central nervous system.

E. A. B. Pritchard, London, *Lancet*, 1935, i, 432 and 448. "Action contracturante de l'acétylcholine sur la musculature striée des malades myotoniques," by A. Lanari, *Comptes Rendus de la Soc. de biol.*, Paris, 1937, **125**, 546. "Biological Thought and Chemical Thought," Linacre Lecture by Sir F. Gowland Hopkins, *Lancet*, 1938, i, 1201. "The Clinical Aspects of the Transmission of the Effects of Nervous Impulses by Acetylcholine," Croonian Lectures by F. R. Fraser, London, *Brit. Med. Jour.*, 1938, i, 1249, 1294 and 1349.

[1] *See* the above footnote on p. 1245.

DESCRIPTION OF PLATE XIX

PLATE XIX

FIG. 1. Muscle-fibres adjoining a wound (three days). ×700. (*a*) Healthy muscle; (*b*) degenerated muscle which is being penetrated and absorbed by both polymorphonuclear leucocytes and mononucleated cells. (From thesis by the late J. W. Dawson, M.D.)

FIG. 2. Muscle almost replaced by phagocytic mononucleated cells. Note the remains of muscle-fibres in the phagocytes. (From thesis by the late J. W. Dawson, M.D.)

PLATE XIX p 1247

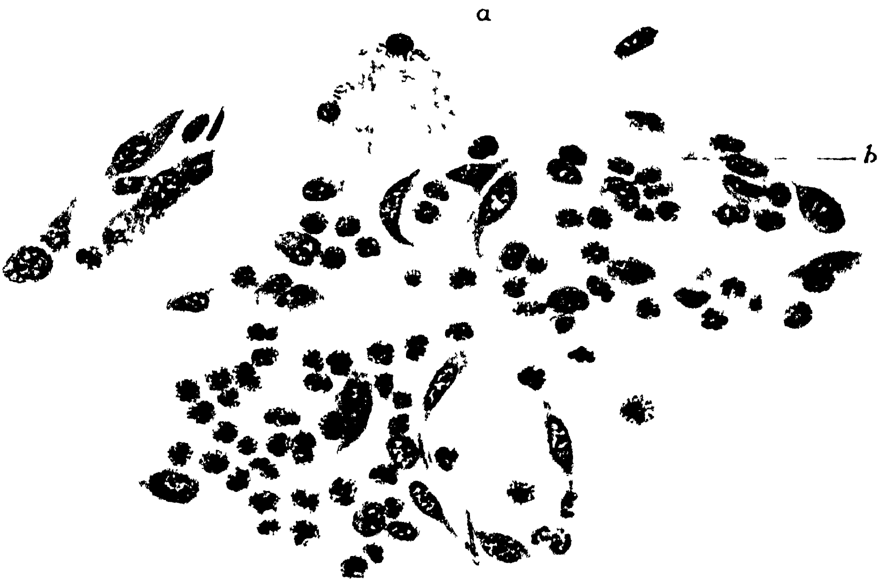

Fig 1.

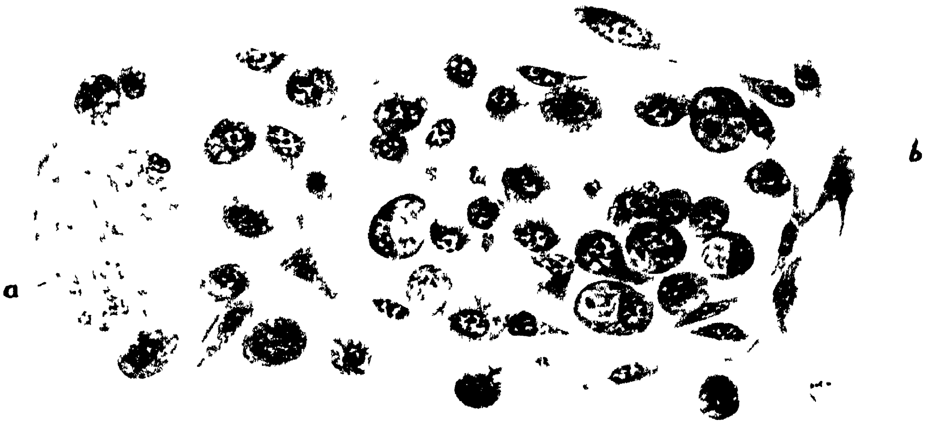

Fig 2.

Peroneal Atrophy (Charcot-Marie-Tooth) (*see also* p. 1172). Like the myopathies, this affection is a hereditary disorder, and occurs early in life, attacking boys much more frequently than girls. It is characterised by bilateral, though not necessarily symmetrical, atrophy of the peroneal muscles, with extension later to the muscles of the calves. The foot becomes dropped and inverted. The associated motor neurones in the cord are atrophied, and degenerative changes have been found in the dorsal columns, in Clarke's column, and occasionally in the cortico-spinal (pyramidal) fibres (Figs. 754 and 755, pp. 1173-4).

Myotonia congenita (**"Thomsen's disease,"** so named after the author who first described it and who himself suffered from the disorder, which was traceable as a Mendelian dominant inheritance in his family for seven generations). In this disease, the fibres of the voluntary muscles are increased in size, but their striation is imperfect and the sarcolemma-nuclei increased in number. It is commoner in the male than in the female, and several members of a family are usually affected. The tonic contractions of the muscles take place more slowly and last longer than in a normal individual. Electrical stimulation also demonstrates this prolongation of contraction. No pathological lesion has been detected in the central nervous system. Nothing definite is known as to its ætiology, and at present the disease is regarded as the result of some congenital defect in the muscles themselves which may not manifest itself until several years after birth.

Myotonia Atrophica. This form of myotonia also is a hereditary disorder, but is associated with progressive wasting of the muscles and their replacement by fibrous tissue and fat. There is no evidence of the presence of any lesion in the central nervous system. Cataract and atrophy of the gonads are stated to occur, and changes in the suprarenals and pituitary have been described. The sternomastoids and other muscles of the shoulder-girdle, and the muscles of the face and upper limbs are those especially affected.

INFLAMMATION IN MUSCLE:—

Various forms of inflammation of muscle are described, but it is sufficient to distinguish between the non-suppurative and the suppurative types.

(*a*) **Non-suppurative myositis** is the result usually of trauma, or is secondary to inflammation of neighbouring structures, *e.g.*, the skin, subcutaneous tissue, bones, joints, and mucous membranes. It is associated with acute and chronic rheumatism and also with trichiniasis (trichinosis or trichinelliasis) (pp. 417-19). It presents the ordinary phenomena of inflammation in other situations, the muscle-fibres becoming swollen, congested and œdematous, and infiltrated with polymorphonuclear leucocytes (Plate XIX, Fig. 1, p. 1246). **Dermatomyositis** is a rare form of non-purulent inflammation of the skin, subcutaneous tissue and muscles, which become œdematous and infiltrated with lymphocytes and plasma-cells. It is associated with tenderness and pain on movement.

In cases in which the inflammatory reaction is due to the irritation of a foreign body such as a bullet, a piece of clothing, catgut-ligatures, etc., and in which sepsis is not pronounced, the muscle-fibres tend to lose their striation, to become homogeneous in appearance, and eventually to disappear. The sarcolemma-nuclei undergo proliferation, and a characteristic feature is the production of large mononucleated (Plate XIX, Fig. 2) and also irregular multinucleated cells—cells concerned apparently in the process of absorption.

(*b*) **Suppurative or purulent myositis** follows suppurative affections in neighbouring structures; or is hæmatogenous in origin—the organisms being carried by the blood-stream and deposited in the muscles, for example in cases of pyæmia, cellulitis, erysipelas, purulent arthritis and gas-gangrene. The

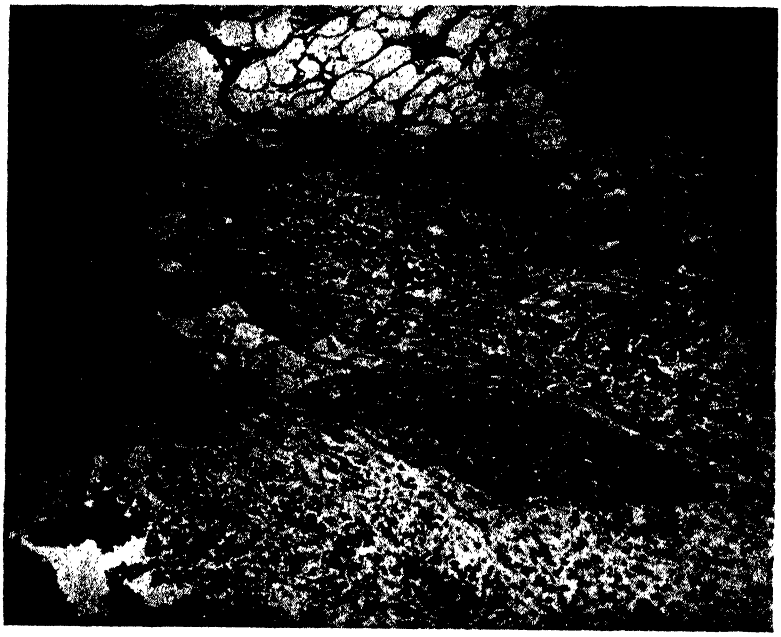

FIG. 800. *Acute Cellulitis in the Subcutaneous Tissue,* showing infiltration with inflammatory cells which extends into the muscle-tissue. Hæmatoxylin and eosin. × 50.

abscess may be small or " miliary " : or the pus may burrow in various directions between, and in, the muscle-bundles ; and the muscle-fibres become swollen, softened, and necrosed.

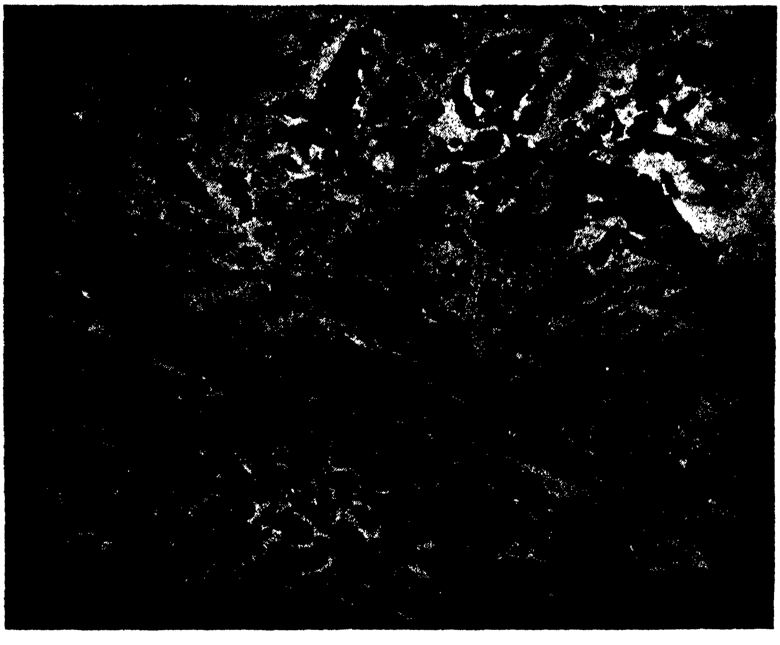

FIG. 801. *Acute Cellulitis in Subcutaneous Tissue,* showing leucocytic infiltration and œdema. Hæmatoxylin and eosin. × 350.

In **gas-gangrene,** anaerobic bacilli of the saccharolytic group, particularl *Clostridium welchii,* invade the muscles and spread widely along both th muscle-fibres themselves and the interstitial tissue. Effusion occurs and the sarcolemma-sheath becomes separated from the muscle-fibres by this fluid, which contains the bacterial toxins. As a result of this separation, the muscle-fibres lose their blood-supply and undergo necrosis. The rapid spread of the disease is due to the growth of the organisms in the muscle-tissue, the constituents of which, including the muscle-sugars, form a culture-medium highly suitable to its growth : and also to the bathing of the tissues in the toxic effusion and the associated extensive necrosis ; but the invasive powers of the organism are *not* always parallel with its toxigenicity, for it has been found that serum-treatment is more efficacious against types of *Cl. welchii* of **high toxicity** than against those of low toxicity but of high invasive power.

In other forms of purulent myositis, any **putrefactive organisms** introduced at the time of the infliction of the wound or which may have gained entrance later, can subsequently develop and give rise to **gangrene.**

In the case of certain muscles, more particularly the **psoas,**[1] and less frequently the **iliacus,** and independently of the spread of inflammation to them from neighbouring structures such as the vertebral column, ilium, sacro-iliac joint, the appendix or any of the pelvic viscera, or from the retroperitoneal lymph-nodes, the occurrence of what has been described as a **"primary abscess,"** usually single, is now recognised as a "clinical entity." Such an abscess may attain a considerable size before it is diagnosed, and is, as a rule, staphylococcal, more rarely streptococcal, in origin.

Fibrositis or **Myofibrositis.** This lesion, which occurs in the fibrous tissue of muscles, and is often described as "muscular rheumatism," is found also in fibrous tissue in other situations, *e.g.*, in the subcutaneous tissues, periosteum, ligaments, tendons (p. 1252) and the sheaths of nerves (*cf.* pp. 1180 *et seq.*, and 1235). The histological changes are characterised by the presence of inflammatory foci, with œdema, the proliferation of the connective-tissue cells of the area, and, at a later stage, the laying down of the new collagen-fibres and associated atrophy of the muscles. Occasionally, areas of necrosis are seen in the fibrous tissue. Apart from the proliferation of the connective-tissue cells, there is little cellular reaction, and that mainly lymphocytic in character. Such histological features are not uncommon in definitely rheumatic affections, *e.g.*, in the "Aschoff-bodies" in the heart (p. 471) and in rheumatic nodules in other situations. Bacteria have not been found in the lesions, which are, however, regarded as originating from chronic infection.

Panniculitis is a similar condition in the fibrous framework of adipose tissue. Severe pain results if the sheaths of the peripheral nerves become involved.

Myositis Ossificans. This disease is characterised by the formation of bone in the muscles. It may result from repeated injuries to a muscle, or a single severe injury, or supervene in degenerative and necrotic lesions which follow acute inflammation. In the process of repair of these damaged parts, granulation-tissue is developed ; and this may undergo "myxomatous" (mucinoid) change, or calcification; or, as just explained, become the seat of actual formation of bone. In some cases following damage to bone or to bone-forming tissues, the osteoblasts may be detached and implanted in the muscle and there continue to function in the production of bone. The muscles most frequently affected are the deltoid and pectoral muscles, the adductors of the thighs, and the other muscles of the arms and legs. The bone develops in the form of irregular nodules, needle-like masses, or plates.

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[1] See review on "Psoasitis, Primary, and Abscess of the Psoas Muscle," by Sir John Fraser, *Medical Annual*, 1940, 382.

Myositis Ossificans Progressiva is a progressive form of the disease found especially in young male subjects, and affects the muscles of the neck, back, and thorax, spreading gradually throughout the entire body. In the early stage, tender doughy swellings appear in the muscles, and these on microscopical examination show definite myositis. The swellings gradually subside, leaving areas of fibrosis in which ossification takes place. The cause of this form is unknown.

Myositis Fibrosa Progressiva. This rare disease, coming on in childhood, is characterised by a transformation of the muscles into dense fibrous tissue. The muscles of the back and upper limbs are those most commonly affected. The condition resembles closely the progressive form of myositis ossificans, but without the occurrence of ossification.

Torticollis or Wryneck. The intermittent spasmodic movements of the muscles of the neck, described as " torticollis," have been classified into several types. Some of these are related to, if not identical with, "trade-spasms" and are often capable of being inhibited voluntarily. If this voluntary inhibition is not exercised, a permanent deformity may be produced. The **neuralgic type,** which is usually associated with pain in the occipital region, with arthritis in a cervical vertebral joint or even with a painful tooth, is characterised by irregular twitchings in the deep muscles of the neck, which cease on the disappearance of the pain, and, even during the painful period, may often be controlled by the will of the patient. The **professional** or **occupational type** is often associated with "writer's-cramp." Kinnier Wilson (1940) states that, in his cases of this double condition, the " writer's-cramp " always " preceded the torticollis, which consisted invariably of spasmodic movements to the right and, as soon as the patient handled his pen, his eyes were taken off the paper by the swing of his head to that side." A similar condition, found in children, may be congenital in origin and is compensatory in character, in order to neutralise some eye-disability such as diplopia resulting from paralysis of certain eye-muscles, especially the external rectus. In the **true congenital type** resulting from birth-injury, the lesion may not be noticed for some months after birth. The head is tilted to one side and the sterno-mastoid muscle of that side is shortened and is seen and felt as a rigid cord. There is no volitional control of the muscle and the lesion is usually associated with a degree of under-development of the face and head on the same side. By many authors, this type is believed to result from hæmorrhage into the injured muscle, with degeneration of the muscle-fibres and subsequent fibrosis—a condition similar to that observed in Volkmann's contracture (see opposite). Other authors, however, hold that interstitial myositis is responsible for the lesion and that the active muscular spasm is due commonly to the unopposed action of a non-paralysed sterno-mastoid drawing the head away from the paralysed muscle. In the **spasmodic type,** there is a loss of voluntary control of the movements, which are irregular and may continue during sleep. Though a single muscle and especially the sterno-mastoid on each side is usually involved, groups of muscles about the face and shoulder may be affected. The condition is always to a greater or less degree bilateral, and both afferent and efferent stimuli are necessary to produce the continuous spasmodic action. The head-movements seen in epidemic encephalitis have been regarded as a variant of torticollis, but there appears to be very little evidence to support this view.

The **paralytic form** commences with a stiffness in the muscles of the neck, followed by paralysis and contracture. Its causation is unknown, but chills, traumatic lesions and infective conditions have been regarded as possible factors in its production.

With regard to the **pathology** of the disease, apart from the histological features which are a sequel to the organisation of a hæmorrhagic or other effusion, and the development of fibrosis, no characteristic pathological picture has been observed. Some writers suggest that lesions of the basal ganglia and especially the corpus striatum are the cause of the spasmodic movements ; but, though in some cases clinical manifestations suggest a lesion in the central nervous system, there is as yet no definite experimental or histological evidence by which this claim can be justified.

Volkmann's Contracture. This deformity of the upper limb was first described by von Volkmann in 1869. In most instances, the development of the lesion has followed fracture at the lower end of the upper arm, especially in children. It has been suggested that, in this fracture, the condyles of the humerus are displaced backwards, and that the periosteum is torn from the proximal fragment and the space so produced becomes filled with blood which infiltrates into the lacerated soft tissues, producing, by pressure on the vessels, an ischæmia with venous obstruction, œdema, necrosis of the muscle-fibres and subsequent fibrosis of the tissues, including the flexor and pronator muscles of the forearm. According to Steindler (1936),[1] the early stage is characterised by a granular degeneration of the muscle-fibres, with loss of striation, leucocytic infiltration, and separation of the fibres by œdema. At a later stage, the damaged fibres are absorbed by phagocytic cells of the histiocyte-series, and are subsequently replaced by fibrous tissue developed during the organisation of the hæmatoma which is formed as a result of the original injury. This new fibrous tissue is distributed irregularly—unaltered muscle-fibres being found side by side with it. Steindler also holds that the sensory manifestations, which are frequently present, are so irregular in their distribution as to suggest that they are due to the circulatory disturbance rather than to direct lesions of the peripheral or sympathetic nerves, a view advanced by some authorities (p. 1182) ; and Horowitz [1] (1942), for example, finds that the communicating channels between the deep and the superficial systems of veins around the elbow are *not* necessarily all obstructed in Volkmann's contracture ; and he suggests that, on the analogy of the reflex ischæmia and venous thrombosis which follow upon trauma of the artery in one variety of "white-leg," these phenomena, including the venous thrombosis, may be partly, or even largely, brought about by reflex vaso-constriction. Analogous lesions in the lower limbs have been described.

Tuberculosis is uncommon in muscles, though they may become infected secondarily from a tuberculous lesion in a neighbouring bone or joint, for example in lumbar and ilio-psoas " cold " or tuberculous abscesses. **Syphilis** sometimes produces gummatous formation or merely chronic interstitial inflammation with the usual absorption of muscle and subsequent fibrous contraction.

TUMOURS in muscle are usually secondary ; though primary sarcomas are described. The fibromas, lipomas, myxomas, and osteomas, found in muscle, take their origin usually from the interstitial fibrous tissue, and not from the muscle-fibres. **Rhabdomyomas** (pp. 314–15)—often teratomatous in origin, or sometimes part of multiple-tumour syndromes, *e.g.* tuberous sclerosis (p. 1134, and *cf.* Fig. 149, p. 314)—and mixed teratomatous tumours containing striped muscle are also found. Sarcomas and carcinomas occur as secondary growths, and commonly are the result of direct spread from tumours in the vicinity.

PARASITES. *Cysticercus cellulosæ* (Fig. 742, p. 1152), Hydatids, and *Trichinella spiralis* (Figs. 237 and 746, pp. 418 and 1155) develop in muscles. These various parasites are described in Chapter XIV, Section II, pp. 397, 400 and 417 respectively.

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[1] A. Steindler, *Surg., Gynec. and Obstet.*, 1936, **62**, 358 ; and T. Horowitz, *ibid.*, 1942, **74**, 871.

DISEASES OF THE TENDONS, TENDON-SHEATHS, AND BURSÆ

Only a brief reference to these is required here, as the subject is fully dealt with in works on Surgery.

RUPTURE OF TENDONS. Tendons may be accidentally cut across or torn from their attachments, or ruptured (*e.g.*, the tendon of the plantaris muscle, the tendo Achillis, etc.), especially if they are the seat of previous disease. Contraction of the corresponding muscle usually leads to pronounced retraction of the proximal part of the severed tendon, and attempts at surgical repair of a tendon thus retracted within its sheath may be disappointing (*see* footnote on p. 973).

DISPLACEMENTS of tendons, *e.g.*, of the extensors of the fingers as they pass over the knuckles, of the biceps from its groove in front of the shoulder-joint, of one of the peronei, or of other muscles, occasionally occur.

HÆMORRHAGE INTO TENDON-SHEATHS sometimes results from injury or from severe inflammation.

INFLAMMATION OF TENDON-SHEATHS, or TENO-SYNOVITIS, may be acute or chronic—dry, with effusion of fluid, or suppurative.

(*a*) **Acute non-suppurative teno-synovitis** may be **traumatic,** *e.g.*, from over-action, or from sprains : or **infective** in origin, *e.g.*, from invasion with the organisms of acute rheumatism, gonorrhœa, etc. (*see* Fibrositis, p. 1249). Gonorrhœal cases are generally suppurative ; but pus is never developed in uncomplicated rheumatic cases. Acute inflammation may occur also in gout. In such cases, the amount of fluid exudate varies greatly.

(*b*) **Suppurative teno-synovitis,** is due to involvement of the tendon-sheaths in infected wounds : to extension into them of local suppurative conditions, *e.g.*, in whitlow [1] : or as a part of a more generalised infection, *e.g.*, in septicæmia and pyæmia.

(*c*) **Chronic teno-synovitis** may be a sequel of acute inflammation : or it may be **tuberculous** or **syphilitic** in origin. The pathological changes in **tuberculous teno-synovitis** are practically identical with those found in tuberculous arthritis. The chief varieties are : (1) a gelatinous form, in which the tendon and its sheath become softened and jelly-like : (2) a variety accompanied by serous effusion : and (3) a form which leads to the production of " chronic abscess." In **syphilis,** the tendons and their sheaths are sometimes the seat of a comparatively acute inflammatory attack, but, more frequently, the process is chronic in character. Gummatous formation occurs in the substance of tendons, and interstitial overgrowth is also a sequel of syphilis.

These various forms of teno-synovitis may be accompanied or followed by the production of adhesions. The intenser forms of inflammation, especially if suppurative, may lead to necrosis of the affected tendon. Cicatricial contraction, producing deformities, also follows in certain instances.

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[1] Whitlow, a corruption of " *whick-flaw*," or " quick-flaw," from A.S. *cwic*, allied to Latin *vivus*, living, sensitive : and *flaw*, a crack or defect.

Calcification follows other degenerative or chronic inflammatory lesions. **Gouty deposits** of urates are found in and around tendons and their sheaths.

TUMOURS OF TENDON. Primary tumours are rare. Myxomas, fibromas, chondromas, osteomas, and sarcomas occur. The capsular tissues round joints, especially the knee and the ankle, the tendon-sheaths and the deep fascia, *e.g.*, in connection with the hands or feet, are sometimes the sites of origin of **parosteal** or **capsular tumours.** They are apparently sometimes osteogenic in character, and, like the analogous giant-celled tumours of bone (pp. 308 and 1227), are composed of large multinucleated cells intermingled with spindle-shaped or polyhedral cells. They vary considerably in their degree of malignancy, but appear usually to be simple in nature ; though occasionally they may take on more rapid local growth, but metastases from them are said to be unknown. They have been described by some writers under such misleading names as " myelomas " and " xanthosarcomas " (*see* p. 1228 and footnote *re* the latter term, and also note on pp. 1262–3), whilst others regard them as non-neoplastic and chronic inflammatory in nature.

" Ganglion." In this condition, cavities, sometimes of considerable size, and containing clear, raw-white-of-egg-like fluid, or, perhaps more characteristically, a transparent colourless material resembling glycerine-jelly, are developed in the neighbourhood of joints and tendon-sheaths—especially about the dorsal aspect of the wrist. Their origin is much discussed. Usually, they have been regarded as narrow-necked diverticula growing from the synovial membranes of joints or of tendon-sheaths. They are, in reality, mucinoid or " myxomatous " in nature, and arise from the connective-tissue elements in the neighbourhood, but not constituting part, of the joints or tendon-sheath.

DISEASES OF BURSÆ :—

Inflammatory conditions of these are of importance clinically, and are fully discussed in surgical textbooks.

Acute bursitis may be non-suppurative, suppurative, or hæmorrhagic. In the first of these, effusion is usually, though not always, a characteristic feature. Chronic bursitis may be secondary to previous acute disease, or it may be tuberculous or syphilitic. Both acute and chronic forms are found in gouty subjects.

Tumours, such as fibromas, myxomas, chondromas, and sarcomas, occasionally arise from bursæ.

" Adventitious bursæ " are developed over bony prominences subject to pressure and irritation, *e.g.*, in cases of bunion, or on the shoulders, necks, or heads of porters who are accustomed to carry heavy weights on these parts. Such false bursæ are very liable to inflammation.

APPENDIX OF ILLUSTRATIONS

The annexed illustrations have, owing to difficulties connected with war-damage, been omitted from the sections of the text to which they belong. They are classified here according to the pages upon which the conditions dealt with are described.

(From p. 333)

Chapter XIII. Special Varieties of Tumour : Simple Rind-Tumours : Lymphangioma :—

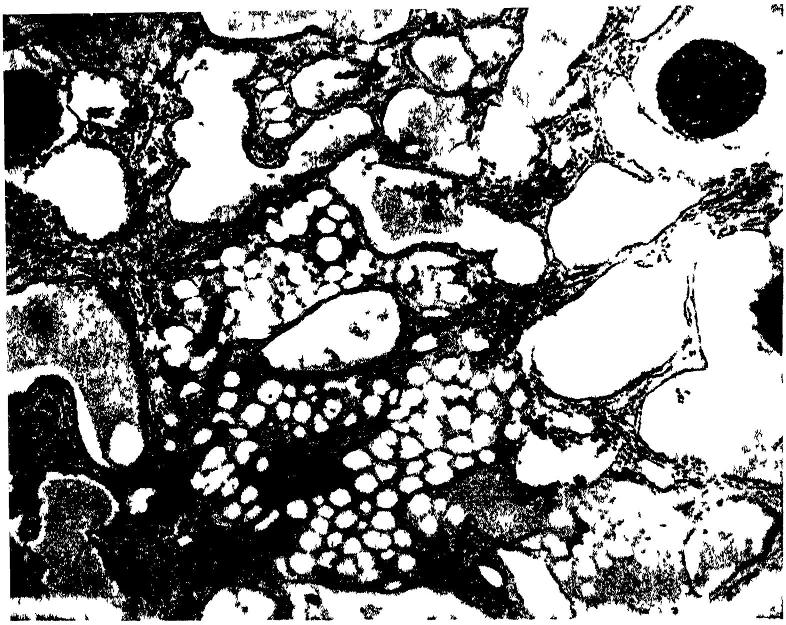

FIG. 165A *Lymphangioma* from subcutaneous tissue of arm, showing irregular spaces containing lymph and lymphocytes. × 60.

(From p. 339)

Chapter XIII. Special Varieties of Tumour : Basal-Celled Carcinoma and Rodent Ulcer :—

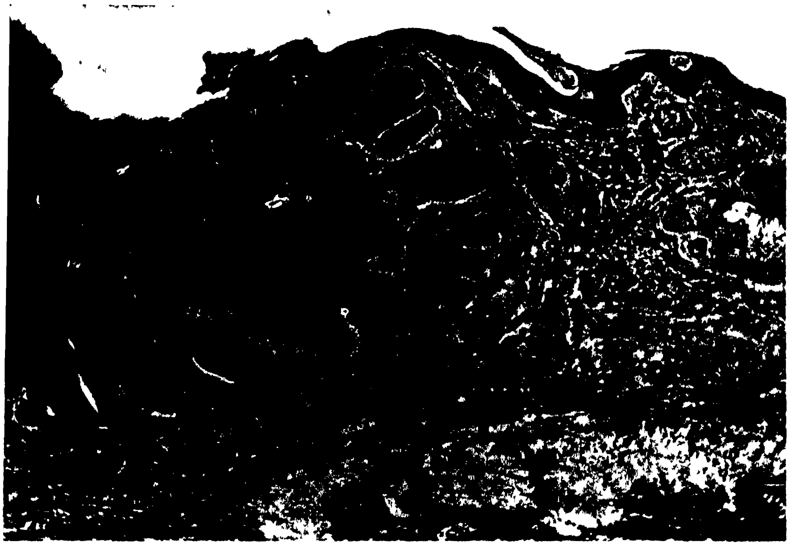

FIG. 171A. *Rodent ulcer of eyelid,* showing downgrowths of epithelium infiltrating the deeper tissues. (Towards the right are seen several normal sebaceous glands.) × 25.

(From p. 810)

Chapter XXIV. Diseases of the Ductless Glands

Pituitary : Hypopituitarism :—

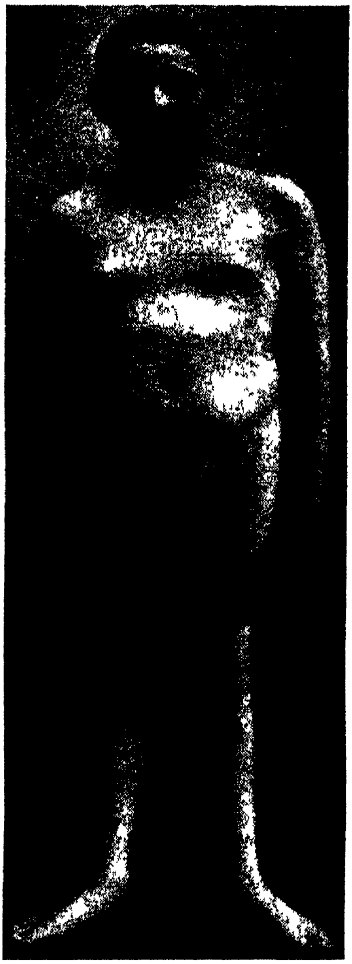

FIG. 462A. "*Adiposo-genital dystrophy*" *of Fröhlich* in a boy of 14, due to compression of the pituitary and interference with the functions of the hypothalamus by a suprasellar cyst (probably a "craniopharyngioma"—the sella itself on X-ray examination appearing to be "normal"). The symptoms were increased sugar-tolerance, polydipsia and polyuria, and gradually diminishing vision with considerable bitemporal hemianopsia, as well as eunuchism with testicular hypoplasia and cryptorchidism and regional obesity. (In the cerebrospinal fluid, there were 11 cells per c.mm., all "small lymphocytes": total coagulable protein 75 mgr. per 100 c.cm.: globulin a trace in excess: chlorides and sugar normal: Wassermann and Meinicke reactions negative.) (Dr. Worster-Drought's case, W.E.H.)

(From p. 810)

Chapter XXIV. Diseases of the Ductless Glands :

Pituitary : Hypopituitarism associated with Compression of Hypothalamic Region :—

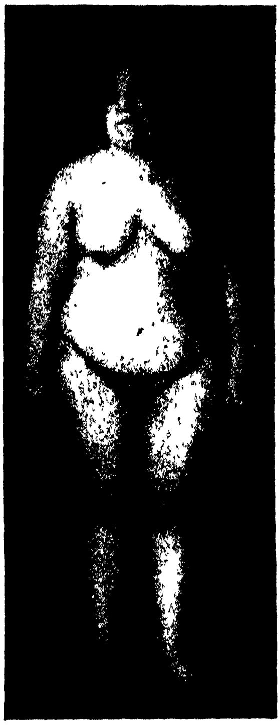

Fig. 462B. *Hypopituitarism of "mixed" type* in a girl of 17 or 18 years. Increasing adiposity first noticed at age of 9, with thirst, polydipsia and polyuria : "fond of sweets," but no sugar in urine. No headache or mental dulness : fundi "normal" and family-history negative. Menstruation commenced at age of 13 and said to be "normal and regular." (W.E.H. case. Note : the records of this case were destroyed by enemy action, but the patient was said to be aged 14 in November, 1934, and the photograph was taken probably in 1937 or 1938.)-

(From p. 836)

Chapter XXIV. Diseases of the Ductless Glands : Thyroid : Tumours :—

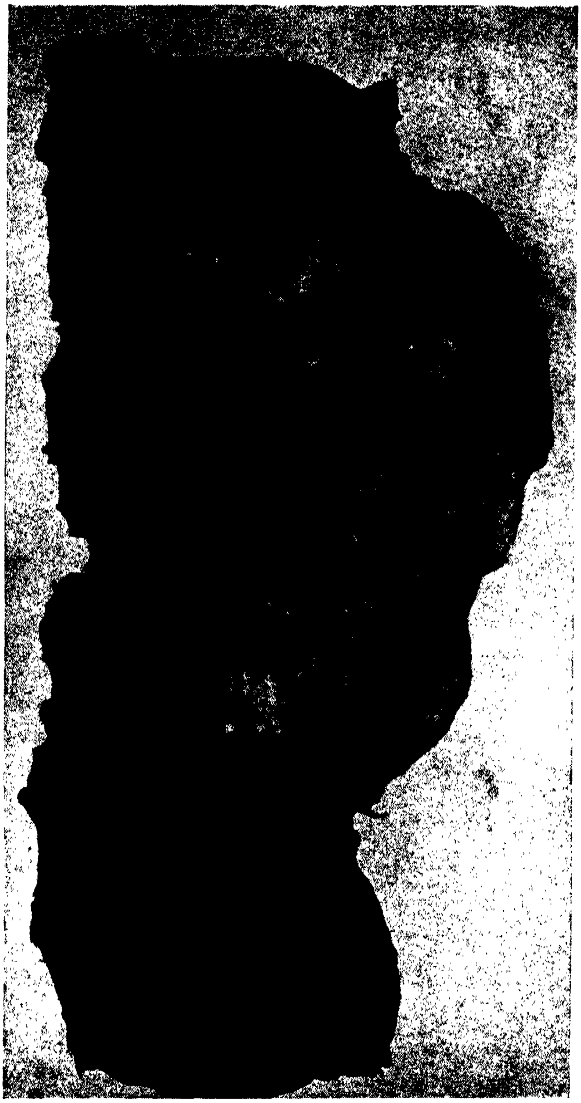

FIG. 486. *Carcinoma of thyroid : invasion of veins.* To the right is seen the jugular vein filled with tumour-tissue, which has extended from a mass in the thyroid adjacent.

(From p. 819)

Chapter XXIV. Diseases of the Ductless Glands : *See* note on the "Laurence-Moon-Biedl Syndrome" below this illustration :—

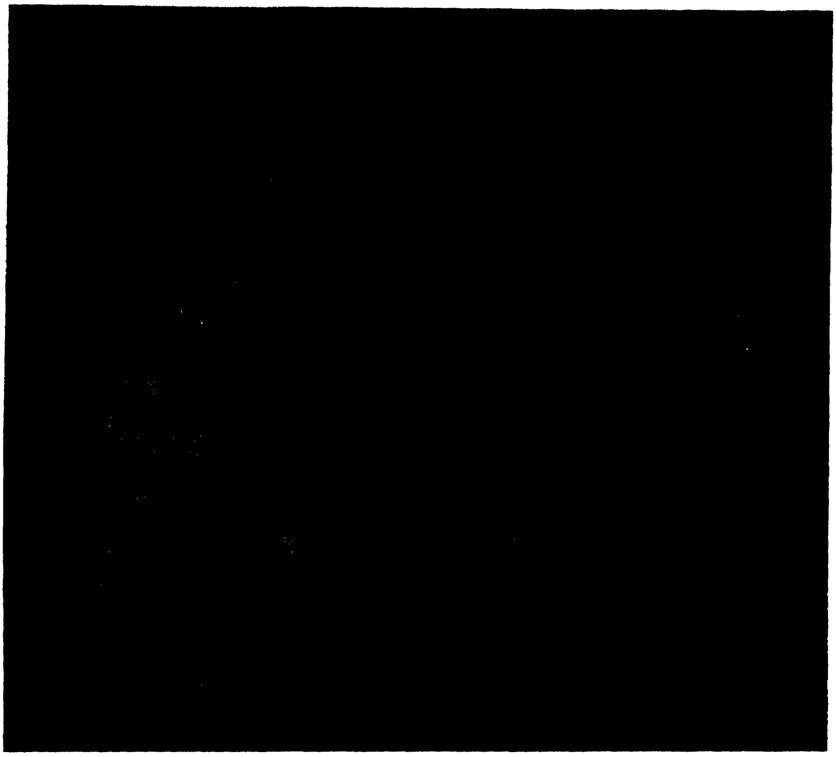

FIG. 494A. *Polydactyly* in a girl aged fifteen years, suffering from the "*Laurence-Moon-Biedl syndrome*," a family-form of adiposo-genital dystrophy characterised by hypogenitalism, obesity, polydactyly, abnormal pigmentation of the retina and failure of vision, and mental backwardness. (W.E.H. case.)

Note on the Laurence-Moon-Biedl Syndrome (p. 819). This is a rare hereditary disorder affecting male children oftener than females, and characterised by obesity, mental retardation, polydactyly, and abnormal retinal pigmentation.[1] Its pathology has not yet been fully investigated, but there is probably some increase in the basiphil, and decrease in the eosinophil, cells of the pituitary, cerebral "atrophy" or, more correctly, incomplete development of the cerebral cortex, especially of the frontal lobes, hypoplasia of the genital organs, and retinitis pigmentosa—one of its most obvious features being the presence of supernumerary digits, both fingers and toes (*see* above Fig. 494A). Hyperostosis of the frontal bone (p. 1260) in this and in certain other varieties of "adiposo-genital dystrophy" has been recorded.

[1] See "Obesity, Hypogenitalism, Mental Retardation, Polydactyly, and Retinal Pigmentation: The Laurence-Moon-Biedl Syndrome," by E. A. Cockayne, David Krestin and Arnold Sorsby, *Quarterly Journal of Medicine*, 1935, **28** (**4** in New Series), 93.

Hyperostosis Frontalis Interna (pp. 1134 and 1226). Bevan Lewis,[1] Sir Thomas Clouston,[2] G. M. Stewart,[3] of Leavesden Hospital, and others, have recorded the occurrence of this " dyscrasia " of the cranial vault in certain cases (especially middle-aged women) suffering from mental disease. Stewart notes its association in these patients with adiposity and changes in the **anterior lobe of the pituitary**; whilst other writers also describe symptoms such as polyuria and polydipsia, and sometimes boulimia, increased glucose-tolerance, glycosuria, narcolepsy and disorders of sleep, and other phenomena associated with disturbed functioning of the **hypothalmus.** The **frontal bone,** chiefly its **inner table,** is the region most often affected, and it may show either a " craggy embossed, or smooth surface,"[2] or in some instances only an isolated osteoma-like projection.

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[1] Bevan Lewis : " Textbook of Mental Diseases," Griffin, London, 1889.

[2] T. S. Clouston : " Clinical Lectures on Mental Diseases," 5th edition, Churchill, London, 1898, pp. 250 and 733 (Plate VI).

[3] G. M. Stewart : " Localised Cranial Hyperostosis in the Insane," *Jour. of Neurol. and Psychopathol.*, 1927–28, **8,** 321.

(From pp. 102–3)

Chapter IV. **Viral Diseases: Herpes Zoster and Varicella.** Cases of herpes zoster coming to autopsy are rare, and the following case of Dr. Worster-Drought's and Dr. Grey Clarke's is therefore of interest, more especially as it also developed a general **varicellar** eruption a week after the onset of the herpes (p. 103). "Hodgkin's disease" had been diagnosed seven years previously at another hospital, but was said to have been " cured by deep X-ray treatment " ; and we therefore cannot exclude the possibility of there having been some antecedent alterations of an unknown character in these ganglia previous to the combined herpetic and varicellar attack during which the patient died with clinical symptoms suggestive of encephalitis—though no characteristic perivascular " cuffing " or demyelination was found microscopically in either brain or cord. The occasional supervention of herpes zoster as a complication or as a sequel of **lymphadenoma,** and also of **lymphatic leukæmia,** is now a well-recognised phenomenon.

Description of Fig. 55A on opposite page :—

(1) *Unstained frozen section* of affected 5th right thoracic spinal ganglion to demonstrate the amount and distribution of the pigment in the cytoplasm of the degenerating nerve-cells, for which see also (5) and (6), and compare Figs. 767 and 768 on pp. 1195–7 illustrating similar phenomena in autonomic ganglion-cells from a patient suffering from Raynaud's syndrome.

(2) and (3) : *paraffin sections* from affected 4th right thoracic ganglion stained by Masson's trichrome method, and :

(4), (5) and (6) : *frozen sections* of 5th right thoracic ganglion treated by Bielchowsky's silver-impregnation method, showing, in the low-power view (4), the widespread distribution of the degenerative changes found throughout the affected ganglia : and, under a higher power, in (2), (3) and (5), (6), the character and details of the degenerative and disintegrative processes in the ganglionic nerve-cells : and also certain (perhaps partly antecedent ?) proliferative changes in the cells of the perineuronal capsules and the " neuronophagy" (p. 1192) of the nerve-cells by these. Note in the nerve-cells the various phenomena of degeneration—condensation and contraction, sometimes amounting to shrivelling, of the cell-bodies (3), in some instances following apparently upon a preliminary swelling of the whole cell (6); aggregation of the cell-pigment immediately around the nucleus in some cells (1), (5), (6), in others its scattering and disappearance throughout the disintegrating cytoplasm (5): the disappearance of nucleus and then of nucleolus in the great majority of the nerve-cells. In fact, the presence of cells still containing nucleus and nucleolus in a comparatively intact state of preservation is exceptional, though isolated examples such as that at the top of (3) were occasionally found; whilst a considerable search was required to find a field such as that shown in (6), containing even a few surviving nucleoli, this group having been

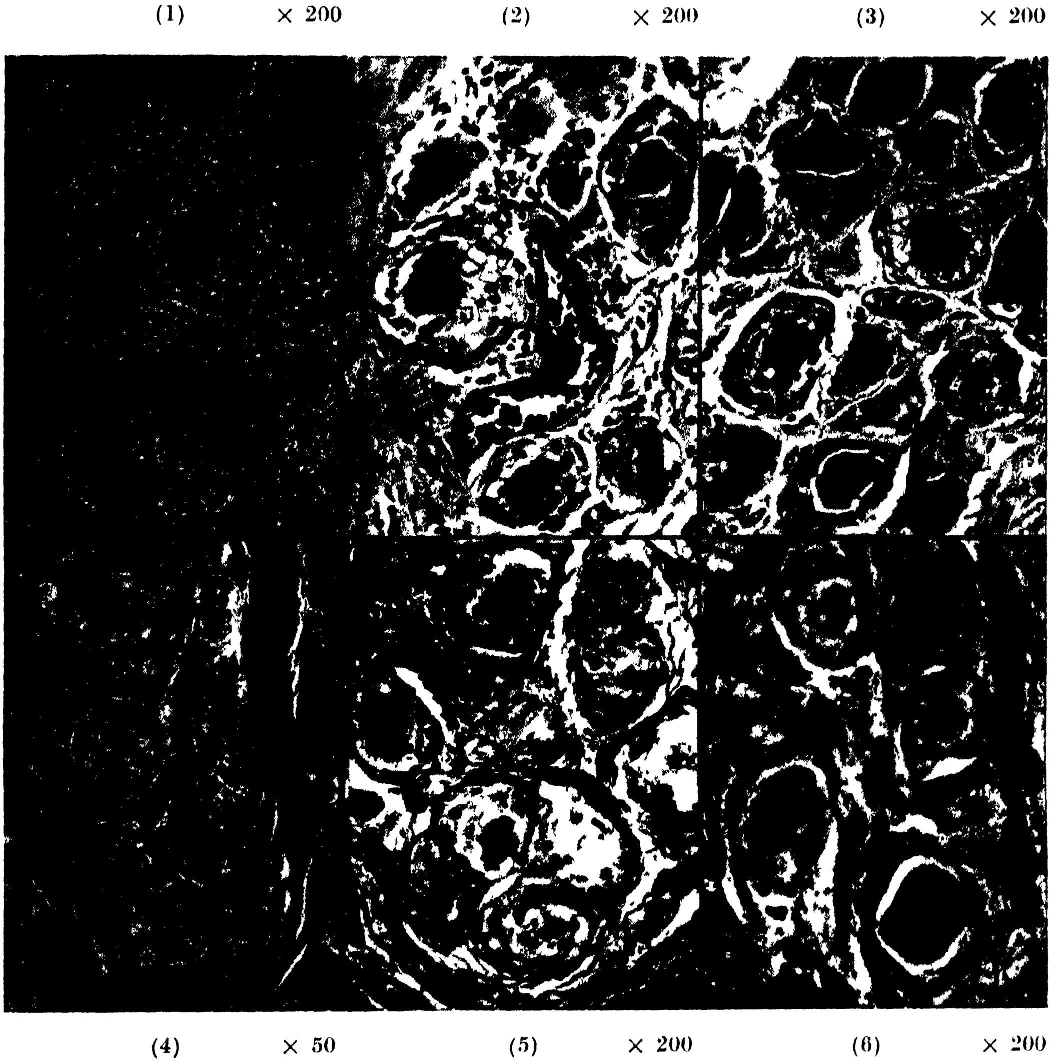

FIG. 55A. Sections of affected *dorsal spinal-root-ganglia* in a case of a man aged 34 years, with *herpes zoster*, and who subsequently also developed *chickenpox*. (For descriptions, *see* opposite.)

selected to illustrate some of the earlier stages or phases of the degenerative process. In (2) and (3) may be noted the congested venule and capillaries, around the former of which there is some slight degree of "small-round-celled" infiltration, which, however, was *not* a special feature of the lesions in the ganglia of this particular case.

(Drs. Worster-Drought, Carnegie Dickson and Grey Clarke's case, Mildmay and West End Hospitals.)

NOTE
ON
THE RETICULOSES AND RETICULO-ENDOTHELIOSES

Since the completion of the text of our book, valuable contributions have been made to the re-classification of certain important conditions of the **Blood and Blood-forming Organs and Tissues** and of allied or cognate **chronic infective, metabolic** and **neoplastic disorders** of the **Reticulo-Endothelial System.** From a study of the histology of the **bone-marrow** (pp. 603, 616), **spleen** (pp. 688–9), **lymph-nodes** (pp. 673–4), and **lymphadenoid tissues** of the throat and gastro-intestinal tract (p. 738 *et passim*), it is well known that these organs and tissues contain **two main sets of elements** likely to be affected by disease, viz. :—

(1) The connective-tissue reticulum with its supporting and nutrient cells—these together constituting portions of the so-called **Reticulo-Endothelial System.**

(2) The **specific cells** of the organ or tissue itself, contained in the meshes of this network, *e.g.*, the **lymphoblastic cells and lymphocytes** of the lymph-adenoid tissues : and the **leucoblastic and erythroblastic elements** of the bone-marrow.

It is natural, therefore, to expect that the pathological changes brought about by toxins, viruses, or irritants of other types, or due to deficiencies in certain food-elements, vitamins and maturation-factors, will lead to the production of changes in these two sets of elements, and that these changes will be analogous, similar, or even identical in the various organs and tissues mentioned, and particularly in the readily-reacting **reticulo-endothelial system**—sometimes widely throughout the body, at other times in one or other or in several of the organs or tissues of which it forms an important constituent part. The nature and degree of the reactions in these "**reticulo-endothelial**" **organs and tissues,** and in their **specific cells,** will, of course, vary with the age of the patient and the functional activity and capacity of his tissues, as well as with the character, virulence and mode of attack of the irritant—subjects which are fully discussed in various sections of our textbook.

The space at our disposal is here too limited to allow of a full discussion of the subject, but an excellent summary of it, with references to some of the more important recent papers, will be found in Hadfield and Garrod's book on

"Recent Advances in Pathology"[1] (1942). The grouping on which the following classification is based was suggested by Robb-Smith[2] in 1938. (The numbers in brackets refer to the pages of our own textbook dealing with these subjects.)

THE RETICULOSES

MEDULLARY RETICULOSIS:—

PRIMARY. (*a*) **Undifferentiated** (p. 311).
(*b*) **Hæmic** (the "Leukæmias") (pp. 625–636, 698–9).
(*c*) **Fibro-myeloid** (Hodgkin's disease or Lymphadenoma) (pp. 676, 695).
(*d*) **Histiocytic** (pp. 30–2, 955–6, etc.).

METABOLIC. **THE GENERALISED LIPOIDOSES** (**Storage Reticulosis: Lipoid Histiocytosis**) (pp. 689, 700, 1071).

Primary:—
- (*a*) *Cerebroside.* Gaucher's Disease (pp. 689, 700, 1071).
- (*b*) *Cholesterol—Phosphatide Mixture.* Niemann-Pick's Disease (pp. 700, 1072).
- (*c*) *Cholesterol and its Ester.* Primary Essential Xanthomatosis:
  1. Mainly in Skeleton. Hand-Schüller-Christian's syndrome (pp. 689, 700, 1071).
  2. Mainly in the Skin. Xanthelasma and Xanthoma (*see* Norman Walker and Percival's "Dermatology," 10th ed., pp. 365–8).
  3. Mainly in the Viscera. Lymphogranuloma Inguinale (pp. 104, 755): Regional Ileitis or Crohn's Disease (pp. 743–4).

Secondary:—

Neutral Fat, Lipoid and Cholesterol. Secondary Xanthomatosis (*see* Hadfield and Garrod's article, p. 44).

FOLLICULAR RETICULOSIS:—

(*a*) **Lymphoid.** "Follicular Lymphoblastoma" (pp. 685–6).
(*b*) **Fibrillary.**

SINUS RETICULOSIS:—

Primary (with proliferation of "littoral" cells lining sinuses in spleen, bone-marrow, etc.).

Infective (with a similar proliferation, *e.g.*, in typhoid, kala-azar, malaria, trypanosomiasis, syphilis, etc.) (*q.v.* in Index).

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[1] "Recent Advances in Pathology," Chapters III and IV, on "The Reticulo-Endothelial System" and "Reticulosis and Reticulo-Sarcoma," by Geoffrey Hadfield and Lawrence P. Garrod. Churchill, London. 1942.

[2] "Reticulosis and Reticulosarcoma: A Histological Classification," by A. H. T. Robb-Smith, St. Bartholomew's Hospital, *Jour. Path. and Bact.*, 1938, **47**, 457.

With this classification in mind, a clearer picture will be obtained of the nature of enlargements and other pathological changes in the spleen, liver and lymph-nodes, and the reactions of the reticulo-endothelial and other components of these organs and of the bone-marrow, and of lymphoid tissue generally (for example, of the mouth, throat and alimentary canal); and a better understanding of the reactive processes at work in **regional ileitis** or **enteritis** (Crohn's disease, p. 743), **lymphadenoma** (Hodgkin's disease, p. 676), **tuberculosis, syphilis** and other **granulomatous diseases** (pp. 55–95) will be gained, and of the histological appearances found in **disorders of the blood-forming organs and tissues,** and of the widespread changes throughout the body in the **lipoidoses** (p. 1071), as well as in the various conditions known as "**xanthelasma,**" "**xanthoma**" and "**xanthomatosis**" (*see* Index), and certain other neoplastic processes.

Robb-Smith[1] has also suggested a similar histological and cytological classification of the Reticulo-Sarcomata (here somewhat modified) :—

RETICULO-SARCOMATA :

A. 1. Syncytial (undifferentiated).
   2. Fibrillary Syncytial (" dictyo-syncytial "[2]).
   3. Fibrillary (dictyocytic[2]).

B. **Differentiation to Hæmic Cells :—**
   1. Lymphoblastic (pp. 311, 319, 603, 684–6).
   2. Lymphocytic (lymphosarcoma) (pp. 311, 318, 685).
   3. Myeloblastic and Myelocytic (myelomatosis, etc.) (pp. 319, 1231).
   4. Plasmocytic (" plasmocytoma " or " plasma-celled myeloma ") (pp. 319, 1231).
   5. Erythroblastic (erythroblastomas, etc.) (pp. 319, 638–40).

C. **Mixed or Polymorphic.**

D. **Histiocytic** (from " littoral " of sinus-lining-cells of spleen, bone-marrow, etc.).

For an account of the normal histology of the Reticulo-Endothelial System and of the organs and tissues of which it forms part, the reader should consult Schafer's " Essentials of Histology," 14th Edition, 1938, edited by H. M. Carleton, pp. 57, 237 *et passim.*

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[1] *Loc. cit.*, p. 473.

[2] From Greek, δίκτυον, *diktuŏn* or *dictyŏn*, a net or network, from δικεῖν, *dikein*, to cast or throw (a net), and δίκτυς, *diktus* or *dictys*, a " netter " or fisherman.

INDEX

(Our thanks are due to Dr. Elizabeth Kornerup and Miss M. Irene Wilson, as well as to Mr. W. J. Bishop, for help in compiling and checking this Index. Main items are emphasised in black type, and cross-references are also given in the text of the book itself. Footnotes are indicated by the letter " *n.*" after the page-number, thus, " 459 *n.*")

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ERRATA AND CORRIGENDA

P. 178, last line of first footnote: *for* " pcnding " *read* " pending."

P. 315, line 8 from top: *for* " primitve " *read* " primitive."

P. 481, line 17 from top: *for* " lower " *read* " outer."

P. 481, line 27 from top: after " over " at end of line, insert hyphen (" over- ").

P. 505, line 20 from top: *for* " Klebs-Lœffler " *read* " Klebs-Loeffler."

P. 589, last line, *after* " developed " *and before* " agglutinins " *insert* " anti-**Rh**."

P. 622, line 25, and p. 1001, line 5 from bottom of page: for " *Listerella* " read " *Listeria* " *monocytogenes*, as amended in 1940 by J. H. Harvey Pirie. This organism has now been isolated from certain cases of *infective mononucleosis* (Robert A. Webb, *Lancet*, 1943, *ii*, 5).

P. 623, line 17 from top: *for* " Löffler's " *read* " Loeffler's."

P. 683, line 13 from bottom: *for* " GLANDULAR FEVER *or* INFECTIOUS MONONUCLEOSIS " *read* " GLANDULAR FEVER *or* INFECTIVE (*or so-called* " *Infectious* ") MONONUCLEOSIS."

P. 1296, column 2, line 1, *for* " **Endoctrine** " *read* " **Endocrine.**"

P. 1305, column 2, line 32, in " explanation of, leukæmias " delete comma.

P. 1316, line 36, *for* " **Klebs-Lœffler** " *read* " **Klebs-Loeffler.**"

P. 1327, 6th line from bottom, *for* " *unerd* " *read* " *under*."

P. 1351, column 2, line 7 from bottom, *for* " 569 " *read* " 568A."

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